NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Talimogene laherparepvec for treating metastatic melanoma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The marketing authorisation for talimogene laherparepvec (T-VEC) is restricted to adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. 57% of people in the OPTiM trial had non-visceral metastatic disease (stage IIIB to stage IV M1a). Can the OPTiM trial be considered to be generalisable enough for decision making?
- Given the recent recommendation of pembrolizumab for metastatic melanoma (TA366 and 357), the ERG considered that this is the most relevant comparator. Pembrolizumab may have higher response rates than ipilimumab but comparative long term overall survival benefits are not yet known because of limited follow up.

What is the Committee's view on the most appropriate comparator(s)? Might some patients be offered watch and wait or other local treatments?

- There was no comparison with vemurafanib or dabrafenib because they were assumed to be reserved for later systemic disease and were only applicable to 50% of patients who are BRAF positive. Is this a reasonable assumption?
- People in the OPTiM trial who had very small lesions (<1 cm^2) were more likely to respond to T-VEC than the overall population. How does this affect the generalisability of the results? Would people with very small lesions be considered for T-VEC? The licence indicates that T-VEC is indicated for unresectable disease.
- There were a number of methodological issues with the trial including potential bias because of limited blinding and unbalanced drop out between the treatment arms. The primary endpoint, durable response rate, is rarely used as a primary outcome in clinical trials (although clinically relevant). Does the Committee consider the trial to be of sufficient quality to assess the effectiveness of T-VEC vs GM-CSF?
- Comparison with other agents is made more difficult by the absence of studies carried out in this particular patient group (Stage IIIB,IIIC and IVM1A).How reliable are comparisons with other treatments?
- The trial demonstrated a 16.6% complete response rate for T-VEC and 25 month median overall survival gain compared with GM-CSF, what is the Committee's view of the likely long term benefit of T-VEC
- The aim of treatment with T-VEC is to prolong overall survival and delay or prevent the development of visceral disease. Among 2,116 individual lesions directly injected with T-VEC 64.3% decreased in size by ≥50% and 47.0% completely resolved. Of 981 non-injected non-visceral lesions, 33.7% decreased in size by ≥50% and 21.6% completely resolved. Of 177 visceral lesions, 15.3% decreased in size by ≥50%, the majority of which 9.0% completely resolved. What is the Committee's view of the importance of the systemic effect of T-VEC?
- There are limited data to support the long-term safety of treatment with T-VEC. Does the Committee consider T-VEC to have an acceptable safety profile compared to other treatments for metastatic melanoma?

Cost effectiveness

- The agreed list price is now different from that in the company's submission (increased from £1445 to £1670 for a 1mL 106 PFU/mL vial or 1mL 108 PFU/mL vial). [redacted]
- The company base case used the modified Korn model to correct for differences in patient characteristics between two pooled ipilimumab trials and the OPTiM trial. The ERG considered it not to be appropriate because it was developed using data from patients with predominantly stage IV M1b and stage IV M1c disease (rather than stage IV M1a disease who mostly feature in the OPTiM trial).
- The original Korn publication included both PFS and OS models, whereas the company used the same modified Korn model for both OS and PFS. Does the Committee agree with the company's approach?
- Taking into account the effectiveness of ipilimumab may vary by stage of disease, the company attempted to correct for this by using the two-step Korn model which has the result of further increasing the estimates of ipilimumab efficacy compared with the efficacy in the ipilimumab trials, and using the modified Korn method. The company considers this to be the 'worst case scenario'. The ERG highlighted that this additional adjustment could mean that the issues associated with using the Korn model are further compounded. Which model does the Committee think is the most appropriate, if any?
- The company's base case ICERs were [redacted] per QALY gained or [redacted] ICER compared with ipiliumumab depending on Korn method used. This was based on the list price for ipilimumab and an estimated list price of £1445 for T-VEC. [redacted]
- The ERG questioned the company's approach of using the exponential trend to predict overall survival for T-VEC because it does not fit the data from the OPTiM trial particularly well, and registry data may not have been correctly implemented

given the stage of disease. What is the Committee's view on how overall survival is modelled?

- At 62 months in the company model there is a sudden unexplained increase in mortality, however the model assumes that all long-term survivors are effectively 'cured' at 10 years. Are these assumptions reasonable?

- The ERG commented that the derived ipilimumab survival trends were not reliable and are inadequate for estimating the cost effectiveness of T-VEC in people with non-visceral metastatic melanoma.

- The ERG's exploratory overall survival projections suggested that the company estimate for the mean overall of patients treated with T-VEC may be overstated by 49% to 59% leading to sizeable increases in the estimated ICERs.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of talimogene laherparepvec within its marketing authorisation for treating metastatic melanoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with advanced (unresectable or metastatic) melanoma	Adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (disease stages IIIB–IVM1a) described within this submission as non-visceral metastatic disease	In accordance with anticipated license	The comparator trials included patients with a mix of stages of diease and fewer than 20% had non visceral disease. The population in the OPTiM trial is therefore not directly comparable with patients in other trials TVEC is only suitable for 'injectable' lesions which the company estimate to be approximately 75% of the population with metastatic non-visceral disease
Int.	Talimogene laherparepvec	Talimogene laherparepvec		T-VEC is a live virus, administered every 2 weeks in key centres of excellence with established oncology units. Staff need to be given specific training to be able to administer T-VEC

Com.	• ipilimumab • vemurafenib (for people with BRAF V600 mutation positive disease) • dabrafenib (for people with BRAF V600 mutation positive disease)	ipilimumab	For patients with non-visceral metastatic disease (stage IIIB-IVM1a), ipiliumumab is considered to be the primary comparator in the submission because BRAF inhibitors are often reserved for those patients with rapidly progressing disease and high disease burden. Further, the assessment of comparative effectiveness using the Korn algorithm presents significant challenges with respect to the BRAF inhibitors.	The ERG considers that the results of a comparison of T-VEC with ipilimumab are clinically meaningful but there is now likely to be a shift towards using pembrolizumab instead of ipilimumab as the first choice treatment option in the first- and second-line setting.
Outcomes	• overall survival • progression-free survival • response rate • time to treatment failure • durable response rate • adverse effects of treatment • health-related quality of life.	• overall survival • progression-free survival • response rate (durable response rate and overall response rate) • time to treatment failure • adverse effects of treatment • health-related quality of life.		The ERG noted that DRR (the primary outcome of OPTiM) is a non-validated endpoint and is potentially prone to bias. The ERG considers TTF is an appropriate endpoint in this trial but noted that TTF is not defined in the same way as PFS in the pivotal trials of ipilimumab .

2 The technology and the treatment pathway

2.1 Talimogene laherparepvec (T-VEC) (Imlygic, Amgen) is a virus that kills cancer cells which is derived from the herpes simplex virus type-1 (HSV-1). T-VEC is injected intralesionally into cutaneous, subcutaneous, and nodal lesions that are visible on the skin, palpable, or detectable with ultrasound guidance. The company noted that it has 2 complementary mechanisms of action: replication that causes cell rupture/lysis and death (intracellular or direct effect) and post-lysis release of tumour-derived antigens and GM-CSF, stimulating a systemic immune response from antigen-presenting cells upon distant tumour sites (extracellular or indirect effect). T-VEC does not currently have a marketing authorisation in the UK. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on T-VEC "for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease" (see Table 2~~Table 2~~).

Table 2 Technology

	Talimogene laherparepvec (T-VEC)	Ipilimumab	Dabrafenib	Vemurafenib
Marketing authorisation	T-VEC does not currently have a marketing authorisation in the UK. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on T-VEC "for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease".	Treatment of advanced (unresectable or metastatic) melanoma in adults	Monotherapy, for adults with unresectable or metastatic melanoma with a BRAF V600 mutation	Monotherapy, for adults with BRAF V600 mutation-positive unresectable or metastatic melanoma
Administration method	Intralesional injection up to a maximum of 4 mL per treatment. The initial recommended dose is at a concentration of 10^6 (1 million) plaque forming units (PFU)/mL. The second dose is 3 weeks later, and subsequent doses are biweekly at a concentration of 10^8 (100 million) PFU/mL. Treatment with T-VEC should be continued for at least 6 months unless the physician considers that the patient is not benefitting from treatment or that other treatment is required. T-VEC may be reinitiated if new lesions appear following a complete response and the physician considers that the patient will benefit from treatment.	3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses.	150 mg twice daily, until the patient no longer derives benefit or has unacceptable toxicity Oral	960 mg twice daily, until disease progression or unacceptable toxicity Oral

Acquisition cost	List price: 1mL 10^6 PFU/mL vial or 1mL 10^8 PFU/mL vial = £1,670.00 (updated from £1445 since the company submission was completed). [redacted]	50mg vial: £3750	28 x 75-mg capsules: £1400	56 x 240 mg tablets: £1750
Average cost of course of treatment	The average cost of a course of treatment was estimated at [redacted] based on the list price stated in the company submission (.e. £1445). Assuming that 2.86mL was used for the first dose and [redacted] for subsequent doses including wastage and assuming [redacted] treatment duration. (OPTiM CSR)	For a 70kg person, 4-dose course: £75,000	£1400 per week	£1750 per week
Abbreviations PFU, plaque forming units; T-VEC, talimogene laherparepvec Source: company's submission, section 2; British national formulary online (December 2015), NICE technology appraisal guidance 268				

See summary of product characteristics for details on adverse reactions and contraindications.

2.2 Malignant melanoma is classified in metastatic sub-stages, which encompass [either]:

- Unresectable stage III disease with regional skin and/or lymph node involvement (M0)

or

- Distant metastatic disease (stage IV), to any site, with location either in:
  - skin (distant cutaneous or subcutaneous tissue) or distant lymph nodes (M1a)
  - lung (M1b)

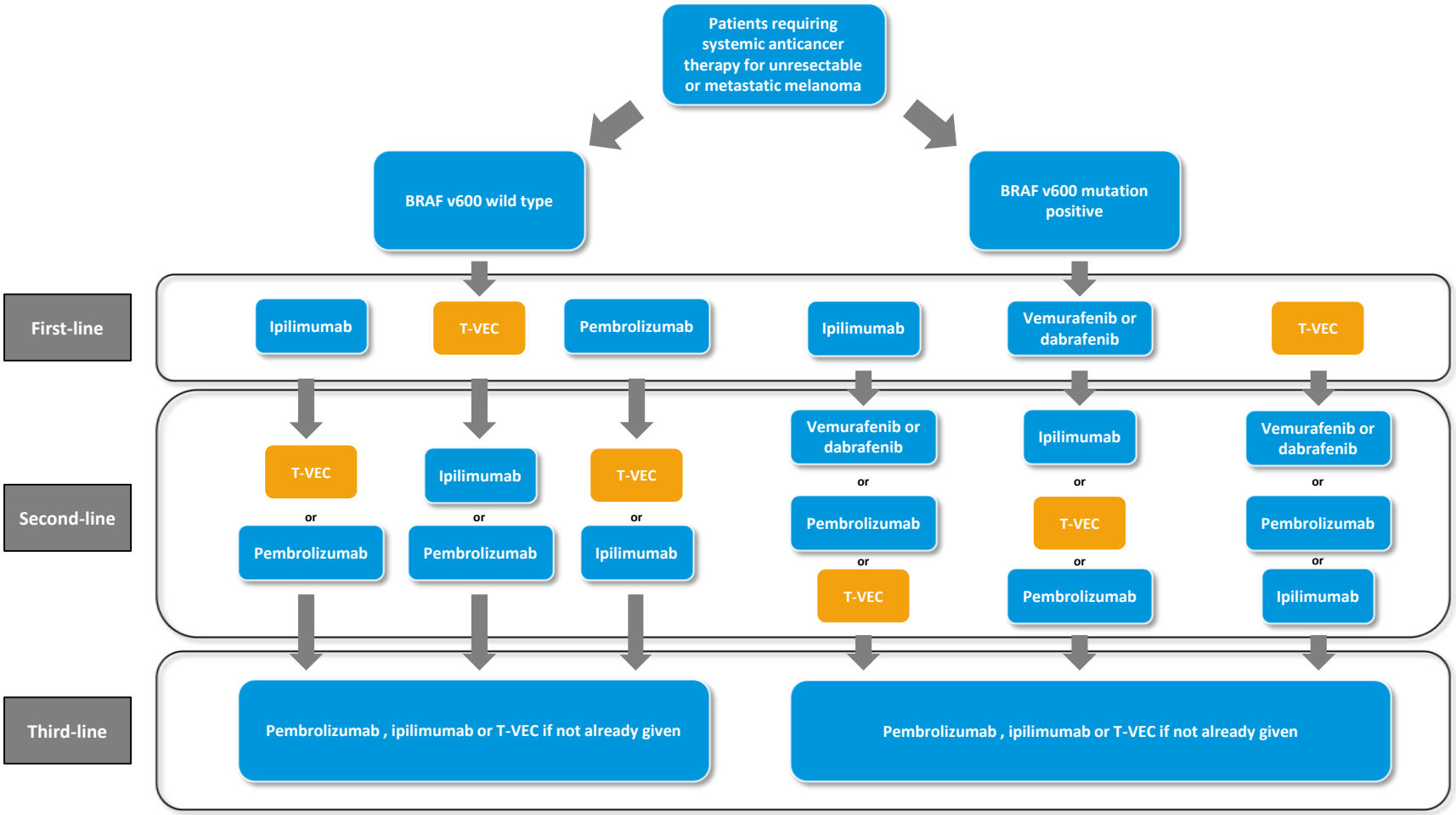
  any visceral organ and/or increased lactate dehydrogenase (LDH) levels in the serum, indicating aggressive tumour growth (stage IV M1c).

2.3 Treatment options for metastatic melanoma include biological therapy, chemotherapy, radiotherapy or surgery. Some people whose disease presents with a BRAF (a protein kinase of the mitogen-activated protein kinase pathway) gene mutation will have targeted therapy. NICE technology appraisals guidance 269 and 321 recommend vemurafenib and dabrafenib as options for treating locally advanced or metastatic BRAF V600 mutation-positive unresectable or metastatic melanoma respectively. NICE technology appraisal guidance 268 recommends ipilimumab as an option for treating advanced (unresectable or metastatic) melanoma in people who have had prior therapy and NICE technology appraisal guidance 319 recommends ipilimumab as an option for treating previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 357 recommends pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma in adults only after the disease has progressed with ipilimumab and, for BRAF V600 mutation‑positive disease, a BRAF or MEK inhibitor and NICE technology appraisal guidance 366 recommends pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab. The company noted

that where immunotherapy/targeted therapy are not suitable, treatment with dacarbazine may be considered. T-VEC can be used at any place in the treatment pathway (see

2.32.4 **Figure 1**~~Figure 1~~) for people with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. The company stated that in clinical practice, people with non-visceral metastatic disease usually have ipilimumab rather than BRAF inhibitors, except where there is evidence of rapidly progressing disease and high disease burden, that is, later stage metastatic disease (stage IVM1b-IVM1c) and so ipilimumab is the most appropriate comparator for T-VEC.

Figure 1 Treatment pathway (Source: company's submission, figure 3-2, page 39)



3 Comments from consultees

3.1 Clinical experts commented that current NHS treatment for with stages IIIB/IIIC/IVM1A melanoma includes local palliative surgery, isolated limb perfusion, immunotherapy (ipilimumab/nivolumab/pembrolizumab) or targeted drugs (BRAF inhibition +/- MEK inhibition). One expert commented that systemic chemotherapy (dacarbazine single agent, dacarbazine plus cisplatin, or carboplatin plus paclitaxel), while another suggested that chemotherapy plays no role in the management of metastatic malignant melanoma. Overall, the currently available treatments do not offer a cure but only palliative extension of life. The clinical experts highlighted that there is an urgent need to improve treatment options for people with melanoma.

3.2 The clinical experts commented that the clinical trials evidence reflected clinical practice including that in the UK. However only a small portion of all people with metastatic malignant melanoma would be suitable for this treatment. The clinical experts state that T-VEC will be easy to use but is time consuming because of the need to repeatedly inject tumour lesions and the need to discard any clinical waste as genetically modified waste. The clinical experts expect that data will emerge over time for the use of this technology with anti-PD1 and anti-CTLA4 antibodies and that this combination may offer future potent further benefit for technology.

3.3 The clinical experts highlighted that use of this technology is likely to be restricted to specialist hospital units with experience of using oncolytic immunotherapies.

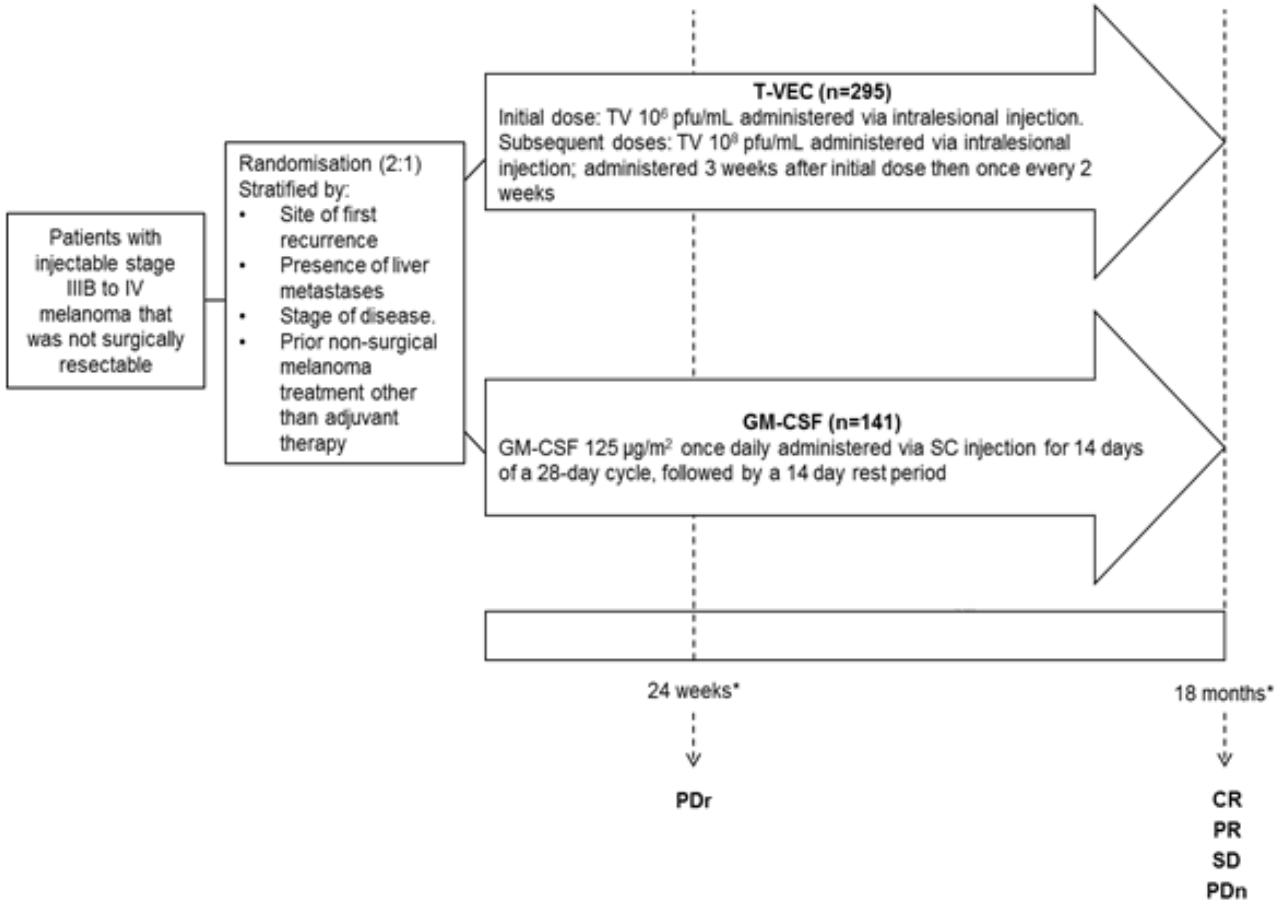
4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company did a systematic review and identified 1 randomised clinical trial, OPTIM. OPTIM was a multinational (including UK), open-label randomised clinical trial that compared intralesionally administered T-VEC

with subcutaneously administered GM-CSF in patients with stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable (n=436). Data for the whole population is included in the company's submission, appendix 1.3 although data and results on the subgroup of patients with stage IIIB-IVM1a (n=249) and non-visceral disease only are included in this document in line with the company's submission and the expected marketing authorisation of T-VEC. The company noted that at the time of study initiation, GM-CSF represented a potential treatment for metastatic melanoma with evidence of efficacy as an adjuvant therapy and with biological plausibility as a comparator, being the product of the transgene expressed by T-VEC. Patients were randomised in a 2:1 ratio to T-VEC (n=295) or GM-CSF (n=141). T-VEC was administered by intralesional injection at an initial dose of 10^6 PFU/mL. Subsequent doses of 10^8 PFU/mL were administered 3 weeks after initial dose and then once every 2 weeks. Total injection volume administered was up to 4.0 mL per treatment session. GM-CSF was administered subcutaneously at a dose of 125 µg/m^2 once daily for 14 days of a 28-day cycle, followed by a 14 day rest period (see Figure 2). Patients who had completed treatment in the 12 month study duration were eligible to enter into a 6 month extension study to assess the long-term safety and efficacy of T-VEC. Pre-planned subgroup analyses included disease stage (IIIB/IIIC versus IVM1a versus IVM1b versus IVM1c), line of therapy (first versus second-line or greater), gender (male versus female), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), HSV-1 status (positive versus negative).

Figure 2 OPTIM study design



Source: company's submission, figure 4-3, page 40

4.2 The company noted that baseline characteristics for the overall patient population and the stage IIIB-IVM1a population were similar. It also noted that in the stage IIIB-IVM1a population, baseline characteristics were generally balanced between treatment groups except for ECOG status of 0 (74% compared with 63% for patients in the T-VEC and GM-CSF groups respectively).

4.3 The primary endpoint was durable response rate defined as partial response or complete response that lasted continuously for over 6 months. Response was assessed using the modified World Health Organization (WHO) criteria by blinded central review. Secondary and exploratory endpoints included overall response rate, overall survival, time to treatment failure, health-related quality of life using the Functional Assessment of Cancer Therapy-biological response modifier (FACT-BRM) questionnaire and adverse effects.

4.4 Although the OPTiM trial was an open-label trial, data for the primary endpoint, durable response rate, were reviewed and confirmed by an independent, blinded Endpoint Assessment Committee (EAC).

ERG comments

4.5 The ERG noted that durable response is not a commonly used endpoint (neither primary nor secondary) in other trials of metastatic melanoma; in the draft EPAR it was noted that this is a new clinically relevant endpoint which has not been validated endpoint and is potentially prone to bias. The ERG also noted that the definition of the primary endpoint allowed a patient to have a durable response despite disease relapse, progressions after 6 months or developing new lesions. However, the ERG concurred with the European Medicines Agency view that durable response rate was an acceptable endpoint because it captures a relevant clinical effect of the treatment.

4.6 The ERG noted that despite the lack of randomisation within the subgroup of people with non-visceral metastatic disease (57%), apart from Eastern Cooperative Oncology Group (ECOG) performance status, the patient characteristics were well balanced for patients with non-visceral metastatic disease. The ERG agreed with the company that baseline characteristics were similar across all patients with non-visceral metastatic disease.

4.7 The ERG noted that in the ITT population, 53.4% of patients in the OPTiM trial had received prior treatment for metastatic melanoma. However, the ERG highlighted that the type of treatment received in the trial differed from what would be available for patients with metastatic melanoma in clinical practice today. It is therefore unclear if similar findings for pre-treated patients in the OPTiM trial could be replicated in clinical practice in England. Overall, the ERG considered that the patient population in the OPTiM trial is generally similar to the population that is likely to be considered for treatment with T-VEC in clinical practice in England.

4.8 The ERG noted that the OPTiM trial was an open-label trial and because of this, the lack of blinding was a concern because perceived beliefs about the relative efficacy of T-VEC may have influenced decision making about whether to stop treatment (particularly in the GM-CSF arm) or being given another therapy. Additionally, clinical assessments of response were subjective, susceptible to investigator bias, and could have ultimately influenced the determination of stable disease, complete response, and partial response. This could have affected the primary endpoint, durable response rate (DRR) and the secondary endpoint of overall response rate (ORR).

4.9 The ERG acknowledged that central confirmation by the independent Endpoint Assessment Committee of durable response would normally be considered to act as a check against bias from a lack of blinding. The ERG highlighted that the extent to which the blinded EAC minimises bias in the OPTiM trial was debateable because the EAC only evaluated

information sent by investigators for patients with investigator-determined CR or PR, or those who reached 9 months on therapy.

4.10 The ERG noted that a higher proportion of patients in the GM-CSF arm withdrew from the study without ever receiving treatment. Having started treatment, the ERG also noted that those in the GM-CSF arm were also more likely to withdraw their consent, which was another potential source of bias and favoured T-VEC.

Clinical trial results

4.11 Analysis of the primary endpoint, durable response rate, at the primary and final data cut off based on external assessment showed that T-VEC was associated with a higher durable response rate compared with GM-CSF (at final cut off 25.2% in the T-VEC group compared with 1.2% in the GM-CSF group; unadjusted odd ratio [OR] 28.6; 95% confidence interval [CI]: 3.9 to 211.5; p<0.0001) (see Table 3~~Table 3~~).

Table 3 Clinical trial endpoints

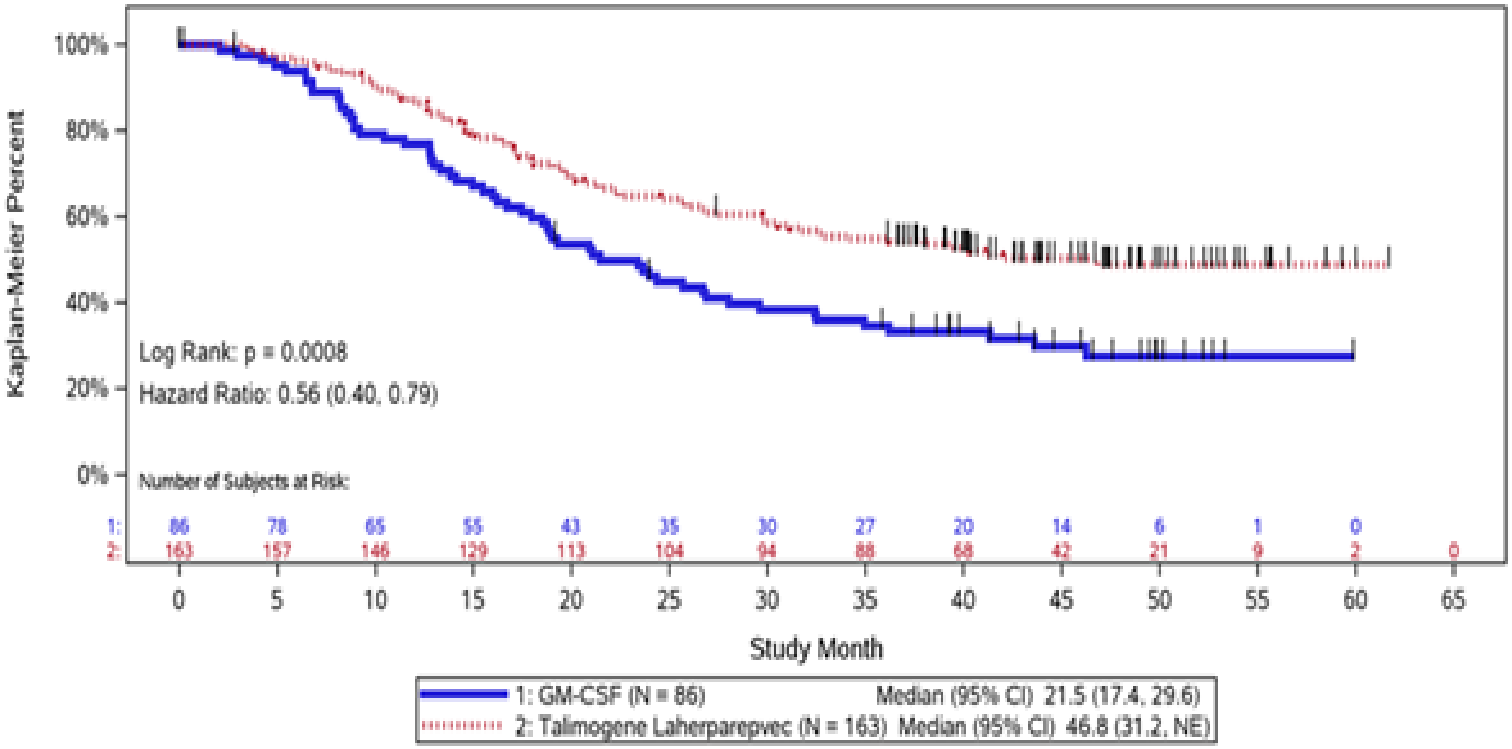
Endpoint	**OPTIM**	
	T-VEC (n=163)	**GM-CSF (n=86)**
Primary data cut – 31 March 2014		
Durable response rate	25.2%	1.2%
OR, p value	28.6, 0.0001	
Median overall survival (months)	41.1	21.5
HR, p value	0.57, 0.0009	
Median time to treatment failure (months) HR, p value	13.1	3.3
	0.27, 0.0001	
Overall response rate (%)	40.5%	2.3%
p value	<0.0001	
Complete response (%)	16.6%	0.0%
Final data cut - August 2014		
Durable response rate	25.2%	1.2%
OR, p value	28.6, 0.0001	
Median overall survival (months)	46.8	21.5
HR, p value	0.56, 0.0008	
Overall response rate (%)	40.5%	2.3%

p value	<0.0001	
Complete response	16.6%	0.0%
Source company's submission, tables 4-13, 4-14, 4-16 and 4-18		

Overall survival was defined as the time from the date of randomisation to the the date of death from any cause. Data on overall survival was censored (that (that is, excluded from analysis from this point onwards) at the last date the the patient was known to be alive when the confirmation of death was absent absent or unknown. Follow up was for 36 months from the date the last patient patient was randomised or until the last patients has died, whichever is earlier. earlier. Results at the primary data cut off showed that T-VEC was associated associated with a 19.6 month benefit in median overall survival compared with with GM-CSF (median overall survival: 41.1 months in the T-VEC group compared with 21.5 months in the GM-CSF group; hazard ratio [HR] 0.57; 95% 95% CI: 0.40 to 0.80; p=0.0009). At the final data cut off (done when all patients patients had been followed for at least 3 years after randomisation), there was was a difference in median overall survival of 25.3 months between the T-VEC VEC and GM-CSF groups (46.8 months in the T-VEC group compared with 21.5 with 21.5 months in the GM-CSF group, HR 0.56; 95% CI: 0.4 to 0.79; p=0.0008) p=0.0008) (see Table 3~~Table 3~~ and

4.12 Figure 3~~Figure 3~~).

Figure 3 Kaplan-Meier curves for overall survival in patients with stage IIIB-IVM1a disease – final data cut off

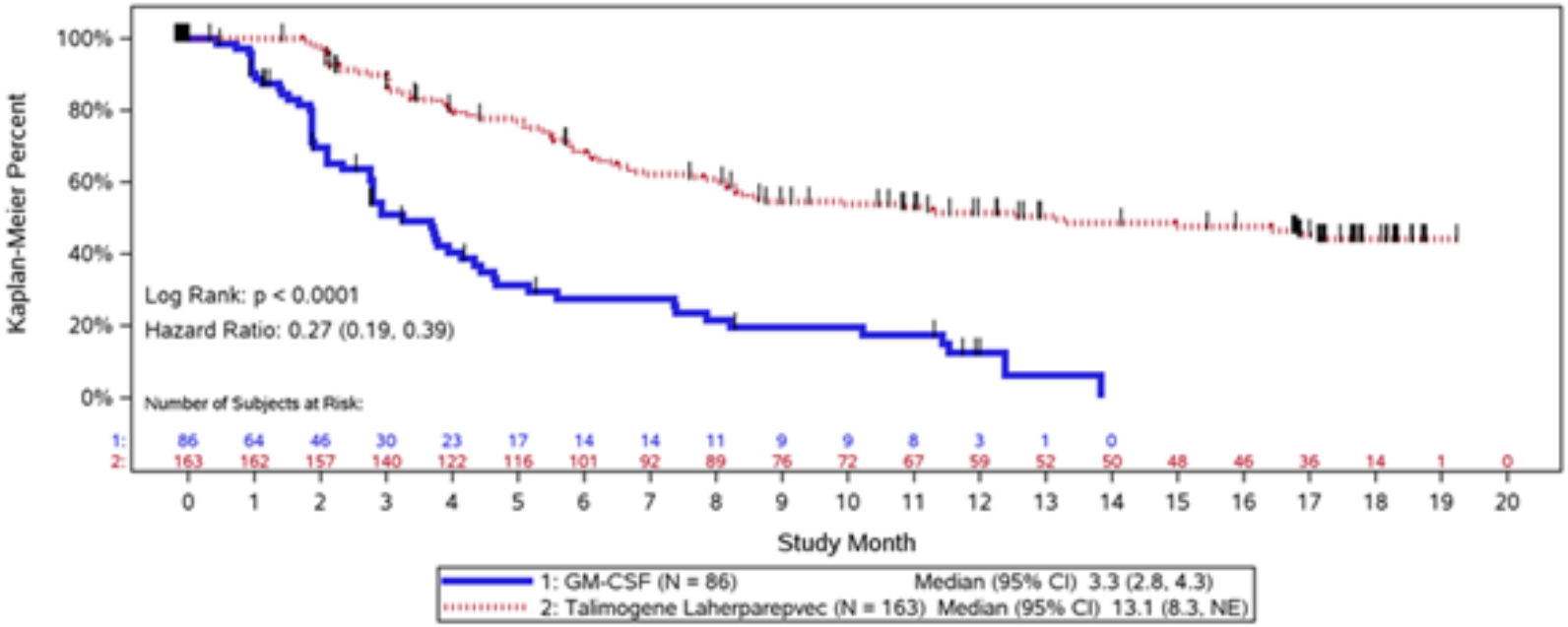


Source: company's submission, figure 4-6, page 69

Time to treatment failure was defined as time from baseline until the first clinically relevant disease progression (where there is no response after the the clinically relevant disease progression). Data on time to treatment failure failure were censored at the last tumour assessment if the patient had not had had clinically relevant disease progression. If there was 1 missed assessment assessment and the next assessment showed clinically relevant disease progression, people in the trial were classified as having the clinically relevant relevant disease progression on the visit date. If there was clinically relevant relevant disease progression following 2 or more missed assessments, data data were censored at the time of the last tumour assessment before the clinically relevant disease progression. The results at the primary data cut off off showed that median time to treatment failure was greater in the T-VEC group (13.1 months) than in the GM-CSF group (3.3 months; HR 0.27; 95% CI: 95% CI: 0.19 to 0.39; p<0.0001) (see Table 3~~Table 3~~ and

4.13 Figure 4~~Figure 4~~).

Figure 4 Kaplan-Meier curves for time to treatment failure per investigator in patients with stage IIIB-IVM1a disease – primary data cut



Source: company's submission, figure 4-7, page 73

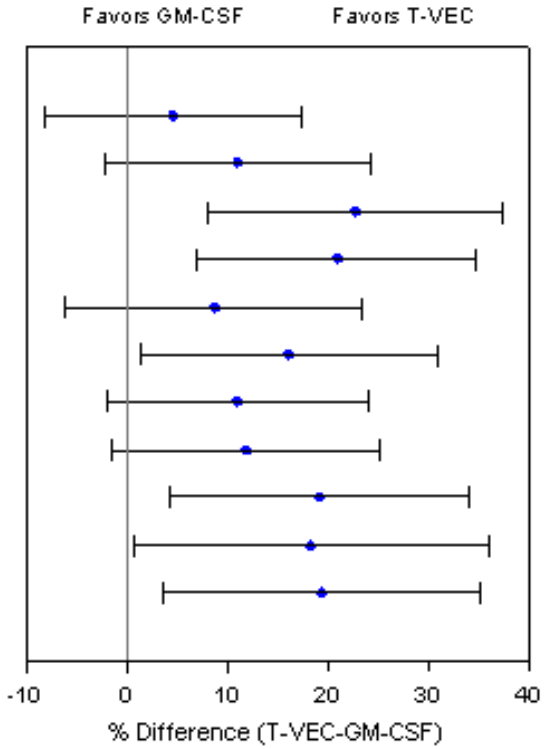
4.14 The company also presented results from exploratory analyses investigating the systemic activity of T-VEC, that is, beyond local effects in injected lesions. Results showed that in analyses of patients with non-injected lesions, 27 out of 79 patients (34.2%) had a more than 50% overall decrease in size in non-visceral lesions, and 8 out of 71 patients (11.3%) had a more than 50% overall decrease in size in visceral lesions. Among 2116 individual lesions directly injected with T-VEC, 1361 (64.3%) decreased in size by more than 50% and 995 (47.0%) completely resolved. Out of 981 non-injected non-visceral lesions, 331 (33.7%) decreased in size by more than 50% and 212 (21.6%) completely resolved. Of 177 visceral lesions, 27 (15.3%) decreased in size by more than 50%. In patients with non-visceral disease, among 1441 individual lesions directly injected with T VEC, 1026 (71.2%) decreased in size by more than 50% and 809 (56.1%) completely resolved. Out of 538 non-injected lesions, 224 (41.6%) decreased in size by more than 50%.

The company presented results on health-related quality of life using the FACT-BRM questionnaire. Improvements in the total score were defined as as increases of more than 5 points from baseline that were sustained for more more than 1 cycle. Improvements in individual domains were defined as increases of more than 2 points from baseline that were sustained for more more than 1 cycle and improvements in individual items were defined as increases of more than 1 point from baseline that were sustained for more than 1 cycle. The company stated that these definitions of improvement were were regarded as clinically meaningful. The company concluded that more more people having T-VEC reported improvements in health-related quality of quality of life compared with GM-CSF (see

4.15 Figure 5~~Figure 5~~).

Figure 5 Improvement rates on the FACT-BRM questionnaire in patients with stage IIIB/C – IVM1a disease

Subscale	N	Rate GM-CSF	Rate T-VEC	% Difference (95% CI)
Trial Outcome Index	207	23.4%	28.0%	4.5% (-8.2% - 17.3%)
FACT-BRM Total	215	26.9%	37.8%	11.0% (-2.2% - 24.2%)
Emotional Well-Being	197	31.6%	54.3%	22.7% (8.1% - 37.3%)
Functional Well-Being	193	25.8%	46.6%	20.8% (6.9% - 34.6%)
Physical Well-Being	130	18.2%	26.7%	8.6% (-6.2% - 23.3%)
Social/Family Well-Being	152	21.6%	37.6%	16.1% (1.3% - 30.8%)
Additional Concerns: Physical	186	20.0%	31.0%	11.0% (-2.0% - 23.9%)
Additional Concerns: Mental	189	22.0%	33.8%	11.8% (-1.5% - 25.2%)
QoL	157	22.4%	41.7%	19.2% (4.3% - 34.1%)
Pain	106	20.6%	38.9%	18.3% (0.7% - 36.0%)
Ability to Work	134	20.0%	39.4%	19.4% (3.5% - 35.2%)



Source: company's submission, figure 4-9, page 77

ERG comments

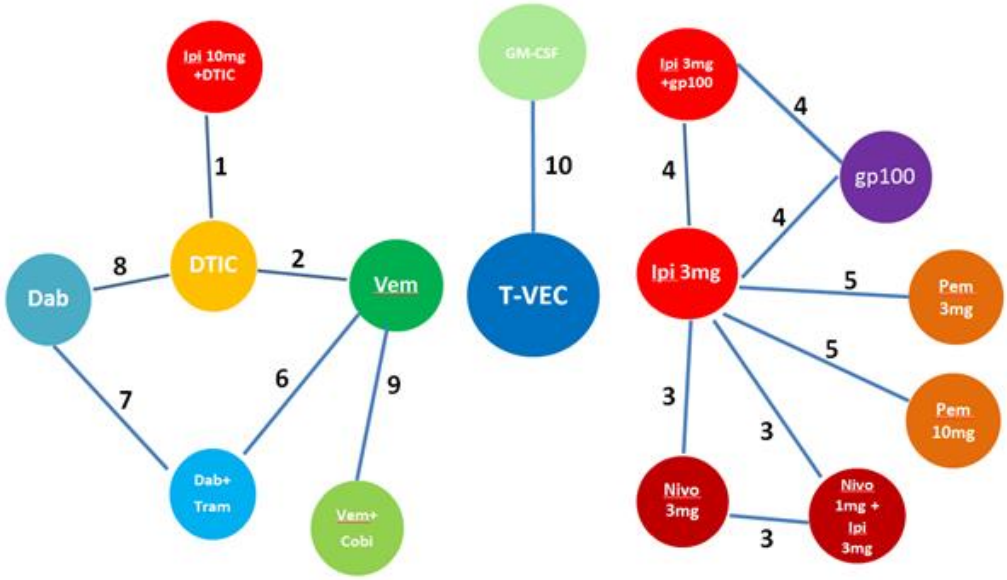
4.16 In the company submission, the results from people with non-visceral metastatic disease were consistent with the results from the ITT population. However, the ERG noted that the magnitude of difference between arms for all endpoints was much greater in patients with non-visceral metastatic disease than in the ITT population.

4.17 The ERG highlighted that the findings for patients with non-visceral metastatic disease are derived solely from an analysis of an exploratory post-hoc subgroup. The ERG's main concern was that the subgroup was a mixture of people with stage III and patients with stage IV M1a disease which are likely to have a different disease trajectory.

Indirect comparison

4.18 The company aimed to do an indirect treatment comparison to compare T-VEC with the different comparators in the scope (ipilimumab, dabrafenib and vemurafenib) but found that there was no evidence that would allow linking an evidence network with any of the comparators. The company reported a disconnected network including 10 randomised-controlled trials (see Figure 6). It noted that there were substantial differences between the patient populations included in OPTIM (in which 57% of patients had stage IIIB-IVM1a disease) and the randomised-controlled trials for the comparators (in which only 11-23% of patients had stage IIIB-IVM1a disease). The company concluded that given the challenges of having a disconnected network and different populations, it was not feasible to do a network meta-analysis.

Figure 6 Network diagram for indirect comparison



Source: company's submission, figure 4-11, page 82

4.19 The company assessed alternative methods to compare T-VEC with the comparators in the scope including a matching-indirect comparison; simulated treatment comparison; adjustment based on the American Joint Committee on Cancer (AJCC) published data and adjustment based on the Korn prediction model. **The Korn model** can be used to predict overall survival using pooled data from 2100 patients from 42 trials done between 1975 and 2005 with different treatments for metastatic melanoma and which included gender, ECOG performance status, presence of visceral metastases, and presence of brain metastases as prognostic factors. The company noted that the Korn prediction model could be used to adjust overall and progression-free survival data from each comparator based on the patient characteristics in OPTIM, so that the adjusted comparator's overall and progression-free survival curves would represent the expected survival if the patients in the comparator trial had similar patient characteristics as those in OPTIM. The company also explored the modified Korn prediction model basing on the approach followed in the company's submission for NICE technology appraisal of ipilimumab for previously untreated advanced melanoma. This modified model included the presence of elevated LDH levels as a prognostic

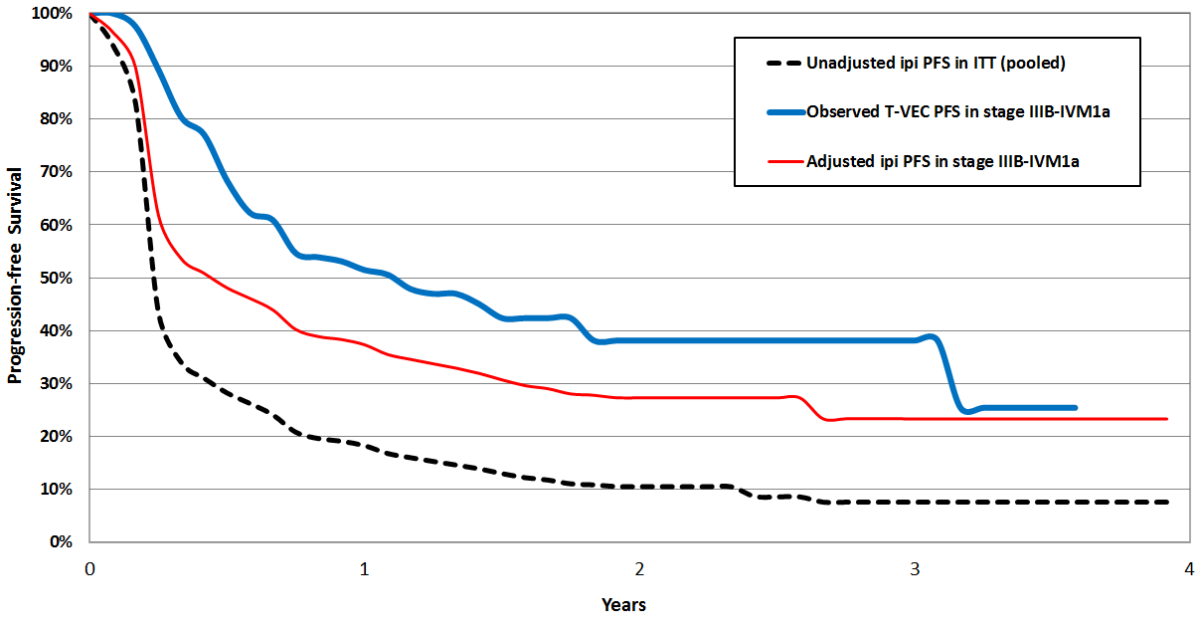
factor. The company stated that the modified Korn prediction model could also be used to adjust overall and progression-free survival data from each comparator. After assessing the feasibility of each method, the company concluded that given the differences in patient characteristics between trials, the patient level data availability and the different prognostic factors accounted for in each method, the modified Korn prediction model was the most appropriate method to compare T-VEC with the different comparators. It stated that using this method was justified because it included key patient prognostic factors, a covariate for presence of visceral disease and had also been used in previous appraisals (NICE technology appraisals 319 [ipilimumab as an option for treating previously untreated advanced (unresectable or metastatic) melanoma] and 366 [pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma].

4.20 The company used the **modified Korn prediction model** to compare T-VEC with ipilimumab only because it considered ipilimumab to be the primary comparator in its submission (see Table 1~~Table 1~~). It included data from OPTIM and 2 randomised-controlled trials for ipilimumab (MDX010-20 and CA184-024 trials). The company noted that it is unknown whether there would be a treatment subgroup interaction for people with non-visceral disease for ipilimumab. It also noted that the modified Korn prediction model captures the prognostic differences between the overall population and the subgroup with non-visceral disease but assumes the absence of potential treatment-subgroup interactions between treatment effect in the overall population and the subgroup of patients with non-visceral disease.

4.21 The company used a 2-step Korn adjustment to account for a potential interaction effect for ipilimumab. The 2-step Korn adjustment accounts for the same prognostic factors but includes an additional adjustment to capture a possible treatment-subgroup interaction effect between ipilimumab and disease stage. Figure 7 – Figure 10 show the results of the modified Korn prediction model and the 2-step Korn adjustment for

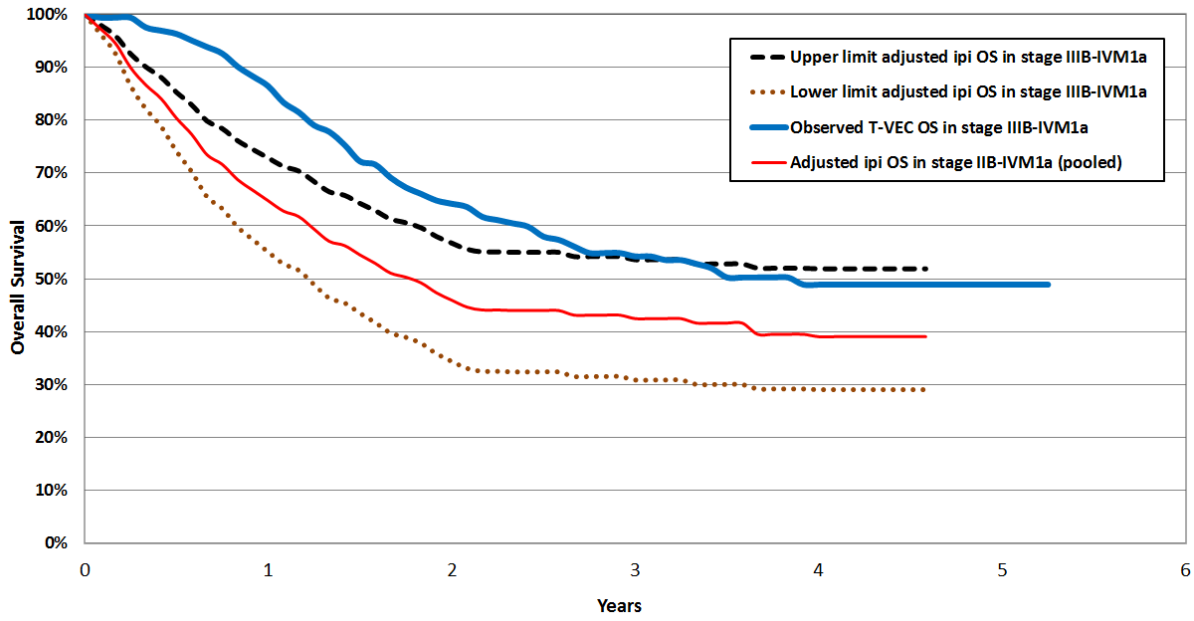
progression-free and overall survival. The company noted that these results were subject to considerable uncertainty because the modified Korn prediction model assumes that differences between studies in all measured and unmeasured confounders are captured by the prediction model and the adjustment factor is assumed to fully represent the degree of difference in the populations. It also noted that the 2-step adjustment method relies on the magnitude of the treatment effect of ipilimumab in the subgroup with stage IIIB-IVM1a disease which is captured by using an estimate of the interaction effect between ipilimumab and earlier stage disease. The company highlighted that the subgroup of patients with stage IIIB-IVM1a disease in the ipilimumab trial included less than 10% of the overall population. The company concluded that based on these analyses, T-VEC was associated with a benefit in overall survival compared with ipilimumab (modified Korn method, see Figure 8) and in the worst possible scenario, with similar overall survival compared with ipilimumab (2-step Korn method, see Figure 10).

Figure 7 Modified Korn adjusted progression-free survival curve for ipilimumab in patients with stage IIIB-IVM1a disease



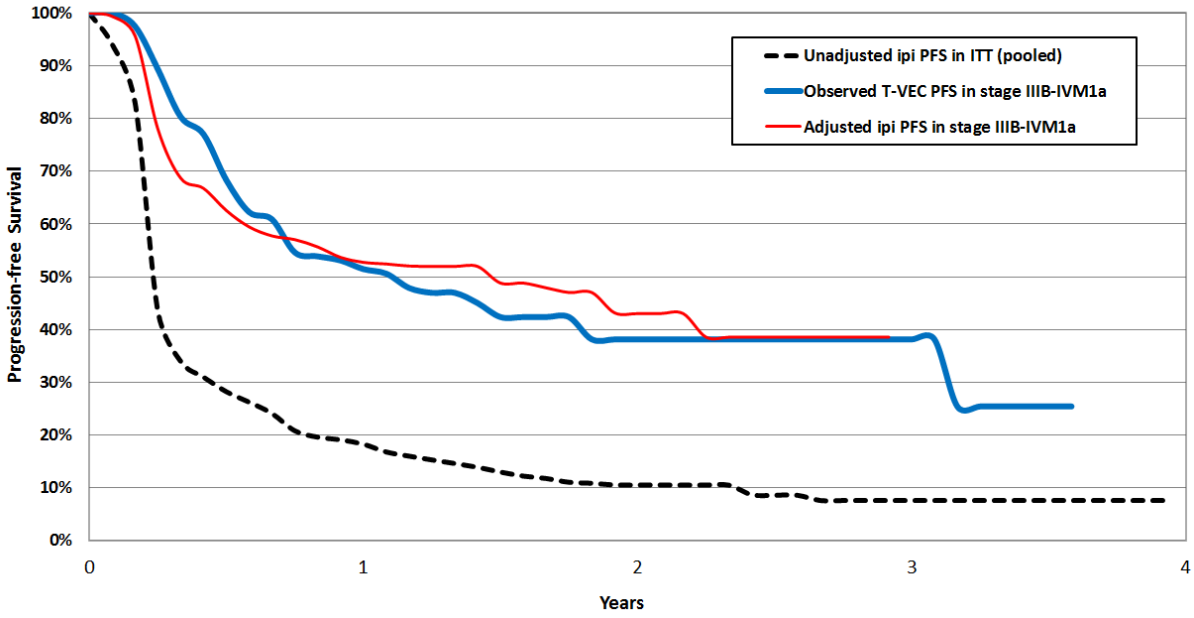
Source: company's submission, figure 4-13, page 92

Figure 8 Modified Korn adjusted overall survival curve for ipilimumab in patients with stage IIIB-IVM1a disease



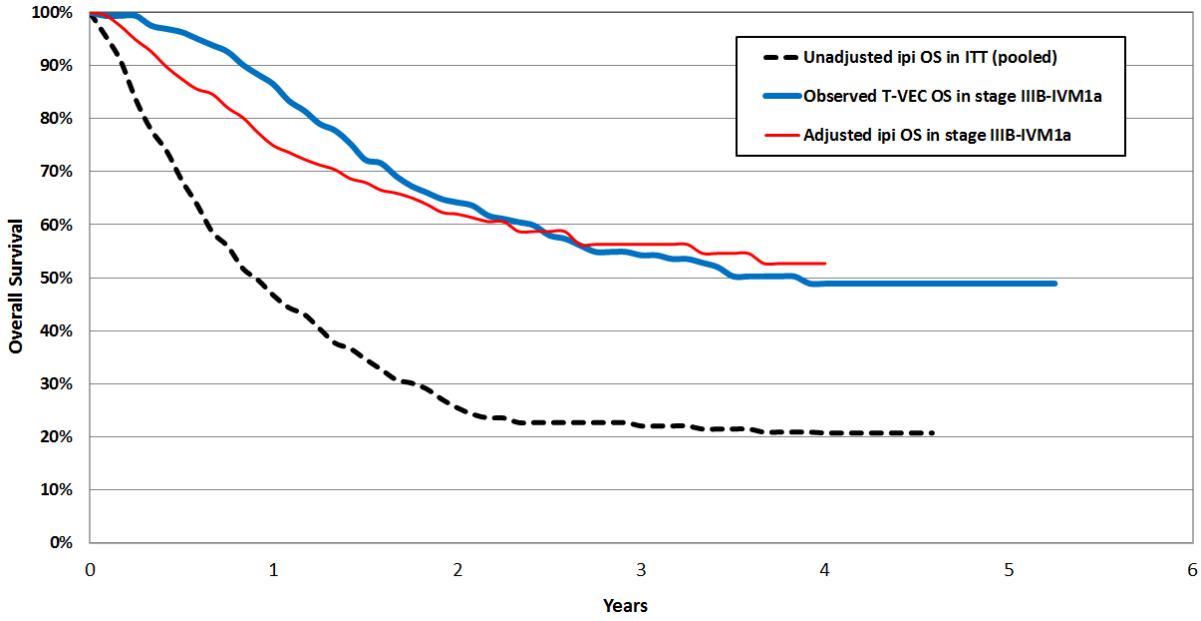
Source: company's submission, figure 4-14, page 92

Figure 9 Two-step Korn adjusted progression-free survival curve for ipilimumab in patients with stage IIIB IVM1a disease



Source: company's submission, figure 4-16, page 96

Figure 10 Two-step Korn adjusted overall survival curve for ipilimumab in patients with stage IIIB-IVM1a disease



Source: company's submission, figure 4-15, page 95

4.22 In summary, the trial results for T-VEC are: median OS: 46.8 months; mean OS: 36.9 months; median TTF: 13.1 months; mean TTF not reached; TTF is considered by the company to be a proxy for PFS. For ipilimumab, the adjusted results, as presented in the company's response to the ERG's clarification letter, were:

- Modified Korn model results for ipilimumab:
    - median OS increases from 10.9 months to 21.3 months (95% prediction interval: 14.6 months to upper interval not reached)
    - mean OS increases from 19.5 to 29.2 months (95% prediction interval: 23.8 months to 34.6 months)
    - median PFS increases from 2.8 months to 5.3 months
    - mean PFS increases from 8.0 to 15.2 months.
- Two-step Korn model results for ipilimumab:

- median OS increases from 10.9 months to median not reached (95% prediction interval: 27.0 months to upper interval not reached)
- mean OS increases from 18.0 to 32.3 months (95% prediction interval: 28.1 months to 35.8 months)
- median PFS increases from 2.8 months to 17.6 months
- mean PFS increases from 7.4 to 18.6 months.

ERG comments

4.23 The ERG noted that that the proportion of people with injectable melanoma in the studies included in the network is unknown. Therefore the characteristics of patients with non-visceral metastatic disease in these trials may differ from those in the OPTiM trial.

4.24 The ERG acknowledged the attempts of the company to consider alternatives to a network meta-analysis to allow survival data from the T-VEC arm of the OPTiM trial to be compared with survival data from other relevant RCTs. The company submission stated that T-VEC was likely to have a greater treatment effect in people with non-visceral metastatic melanoma than in the wider population of patients with all stages of metastatic disease. The ERG agreed that the OPTiM trial evidence appeared to support this and agreed that this observation could be taken into consideration when choosing the most appropriate indirect comparison method.

4.25 Given the lack of clinical effectiveness evidence available, the ERG considered that the company was correct to attempt to apply alternative approaches for the comparison of T-VEC with ipilimumab. However, the ERG did not consider that the use of either of the Korn models was appropriate (see section 5.9 below for the ERG's comments on how this was implemented into the company model). The ERG suggested therefore that the relative clinical effectiveness of T-VEC compared with ipilimumab was unknown. The ERG highlighted that T-VEC does

however, appear to have a better safety profile than ipilimumab pembrolizumab.

Adverse effects of treatment

4.26 The company noted that the incidence of all treatment-emergent adverse events experienced by patients with stage IIIB-IVM1a was higher in the T-VEC group (99%) compared with the GM-CSF group (93%). The incidence of serious adverse events and treatment-related adverse events were also higher in the T-VEC (serious adverse events 20%, treatment-related adverse events 93%) compared with the GM-CSF group (serious adverse events 13%, treatment-related adverse events 79%). The company also noted that treatment-emergent adverse events leading to stopping treatment were comparable between the T-VEC group (9%) and the GM-CSF group (7%). It also added that there was 1 fatal adverse event in the T-VEC group although this was not related to treatment. Treatment-emergent adverse events that occurred with an incidence of more than 5% in the T-VEC group compared with the GM-CSF group included fatigue. Table 4 includes the most common treatment-related adverse events.

Table 4 Summary of treatment-related adverse events in patients with stage IIIB-IVM1a disease

Preferred term	Stage IIIB-IVM1a disease			
AE[a]	T-VEC (N=163)		GM-CSF (N=76)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Chills	49.1	0	3.9	0
Fatigue	44.8	1.8	31.6	0
Pyrexia	38.0	0	7.9	0
Influenza like illness	33.7	0.6	9.2	0
Injection-site pain	28.2	1.2	6.6	0
Nausea	25.2	0.6	11.8	0
Myalgia	17.2	0.6	5.3	0
Pain	14.7	0.6	9.2	0
Vomiting	12.9	0.6	5.3	0

Preferred term	Stage IIIB-IVM1a disease			
AE[a]	T-VEC (N=163)		GM-CSF (N=76)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Headache	12.9	0.6	7.9	0
Arthralgia	12.9	0.6	5.3	0
Diarrhoea	10.4	0	5.3	0
Pruritus	6.7	0	11.8	0
Injection-site erythema	6.1	0	19.7	0
Injection site reaction	3.7	0	11.8	0

Abbreviations: AE, adverse event; GM-CSF, granulocyte macrophage colony stimulating factor; T-VEC, talimogene laherparepvec.

[a] Treatment-emergent AEs by preferred term of any grade with incidence ≥10% in either group and/or grade 3 to 4 AEs with incidence of ≥2% in either group.

Source company's submission, table 4-34, page 107

4.27 A crude comparison of T-VEC with ipilimumab, vemurafenib and dabrafenib, rates of dose discontinuations and/or modifications identified with these other agents are reported in the company submission (pages108-109 and table 4-48). These data showed that T-VEC compared favourably in terms of safety with other recommended treatments for metastatic melanoma.

ERG comments

4.28 The ERG noted that although the OPTiM trial suggests that T-VEC's safety profile compares favourably with the comparators in the NICE scope, there are limited data to support the long-term safety of treatment with T-VEC.

4.29 The ERG agreed with the company that treatment emergent adverse events, serious adverse events and treatment-related adverse events were higher in the T-VEC arm than in the GM-CSF arm. The ERG noted that treatment discontinuation rates due to adverse events were marginally higher in the T-VEC arm than in the GM-CSF arm in the overall safety population.

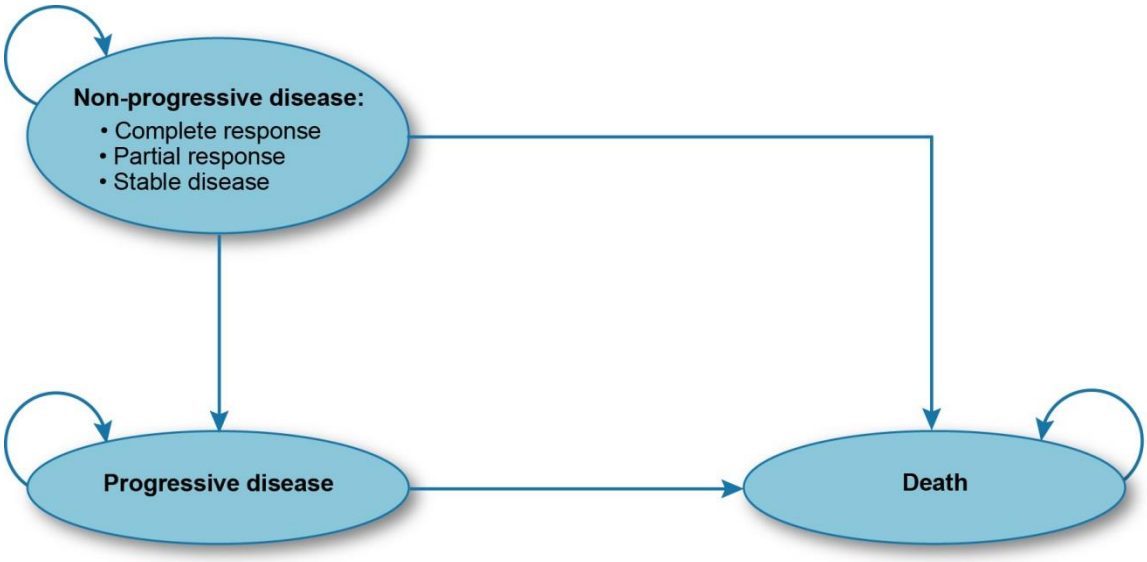
5 Cost-effectiveness evidence

Model structure

5.1 The company did a de novo partitioned survival model to compare the cost-effectiveness of T-VEC with ipilimumab in people with unresectable regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease, that is, patients with stage IIIB-IVM1a disease. The perspective was that of the NHS and Personal Social Services. The time horizon was lifetime (30 years), the cycle length was of 1 week and a half-cycle correction was applied. Costs and outcomes were discounted at 3.5% per year.

5.2 The model included 3 states: non-progressive disease (including complete response, partial response and stable disease), progressive disease (defined as an increase of more than 25% in the sum of the surface areas of all measurable tumours, or an increase of more than 25% in a single lesion or the appearance of a new lesion) and death (see Figure 11). The company assumed that patients enter the model in the non-progressive disease state and have treatment with T-VEC or ipilimumab. Transition to another state depends on response to treatment. After disease progression, patients have best supportive care (BSC) defined as non-curative health care and palliative care. The company assumed that treatment with T-VEC was every 2 weeks for a mean duration of [redacted]. The company assumed that treatment with T-VEC continued for at least 6 months after disease progression. For ipilimumab, the dosing was based on a previous NICE appraisal (TA319) (treatment every 3 weeks for a mean duration of 10.5 weeks) and was lower than that stated in the summary of product characteristics. The use of subsequent therapies was not included in the model. It was assumed that patients who died had had palliative care for up to 3 months before death and terminal care.

Figure 11 Company's model structure



Source: company's submission, figure 5-2, page 124

ERG comments

5.3 The ERG noted that variants of the company model structure have been used previously in the modelling of advanced melanoma for previous STAs (Vemurafenib for treating locally advanced or metastatic BRAF mutation‑positive malignant melanoma [TA269], Ipilimumab for previously untreated advanced [unresectable or metastatic] melanoma [TA319], Dabrafenib for treating unresectable or metastatic BRAF mutation positive melanoma [TA321].

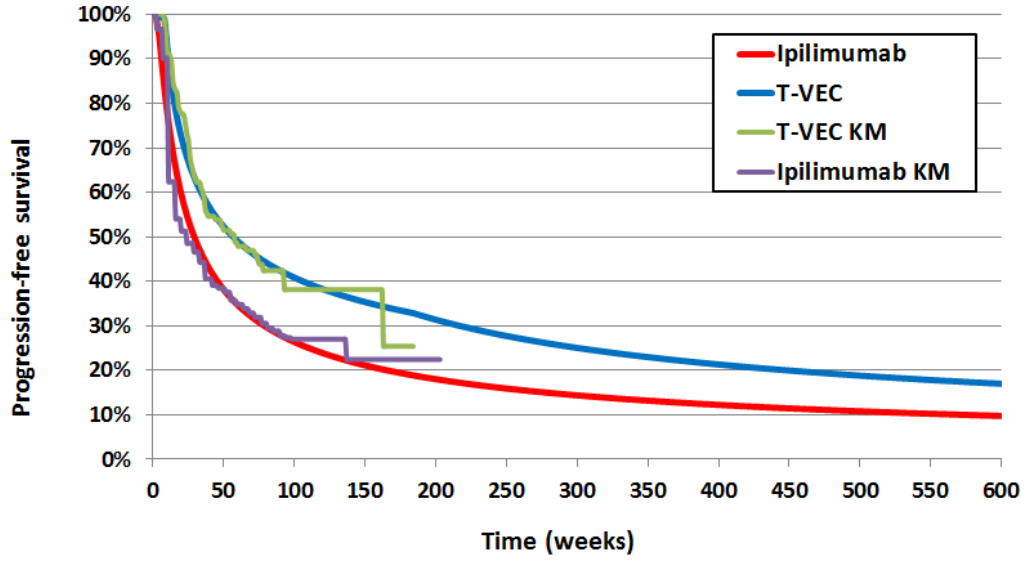
Model details

5.4 Clinical inputs were taken from OPTIM, CA184-024 and MDX010-020. The company used data from the final data cut off from OPTIM for T-VEC and pooled the published clinical trial data for ipilimumab from CA182-024 and MDX010-020. The company used the progression-free and overall survival results from the modified Korn prediction model and the 2-stage Korn adjustment in the model (see section 4.13). The mean age of patients in the model was 64 years.

5.5 The company applied different parametric curves to extrapolate progression-free survival data in the model and concluded that the

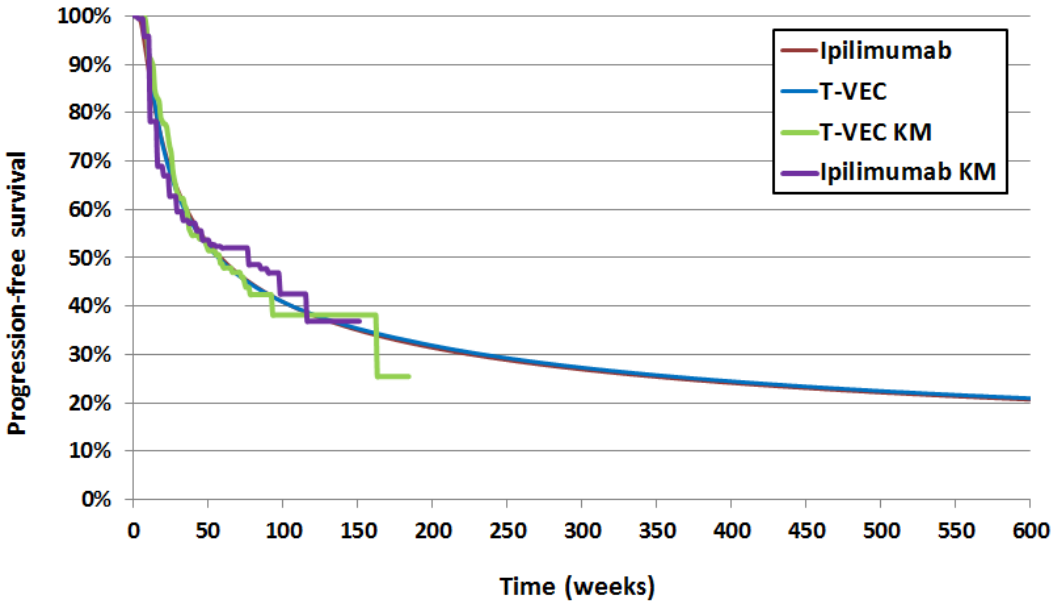
generalised gamma distribution provided the best fit to the data for T-VEC and ipilimumab. Figure 12 and Figure 13 show the progression-free survival estimates used in the model based on the modified Korn prediction model and the 2-stage Korn adjustment respectively. The company stated that because of the lack of data of ipilimumab for people with non-visceral disease, there is uncertainty about the treatment effect of ipilimumab in the population considered in the model (see section 4.13).

Figure 12 Progression-free survival estimates for T-VEC and ipilimumab (based on Modified Korn adjustment)



Source: company's submission, figure 5-26, page 146

Figure 13 Progression-free survival for T-VEC and ipilimumab (based on 2-step Korn adjustment)



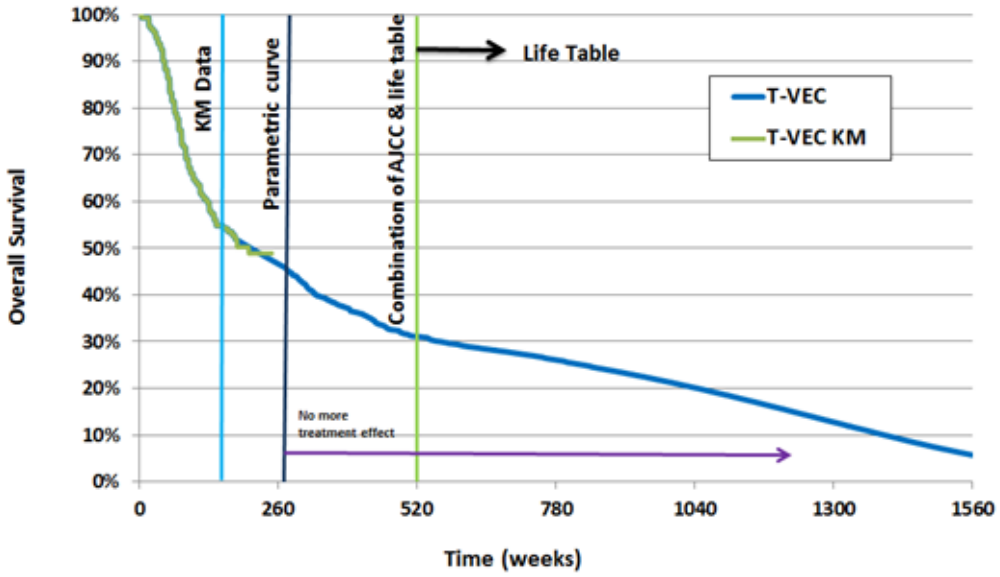
Source: company's submission, figure 5-27, page 146

5.6 The company modelled overall survival using a 3-part curve fit based on changes on the slope of the overall survival Kaplan-Meier curves:

- First part of the 3-part curve fit (until 40.7 months for T-VEC and until 29.7 months for ipilimumab): the company used Kaplan-Meier overall survival data from the trials
- Second part of the 3-part curve fit from the start of the data cut until the end of observed trial data (62 and 55 months for T-VEC and ipilimumab respectively): the company applied different parametric curves to the overall survival Kaplan-Meier data from the modified Korn prediction model and the 2-stage Korn adjustment and concluded that the exponential distribution provided the best fit for T-VEC and ipilimumab
- Third part of the 3-part curve fit (from 62 and 55 months for T-VEC and ipilimumab respectively to 10 years): the company used observational disease-specific data from the AJCC registry based on the publication from Balch et al (2009) and mortality data from life tables published by the Office of National Statistics. Data from life tables alone was used from year 10 onwards.

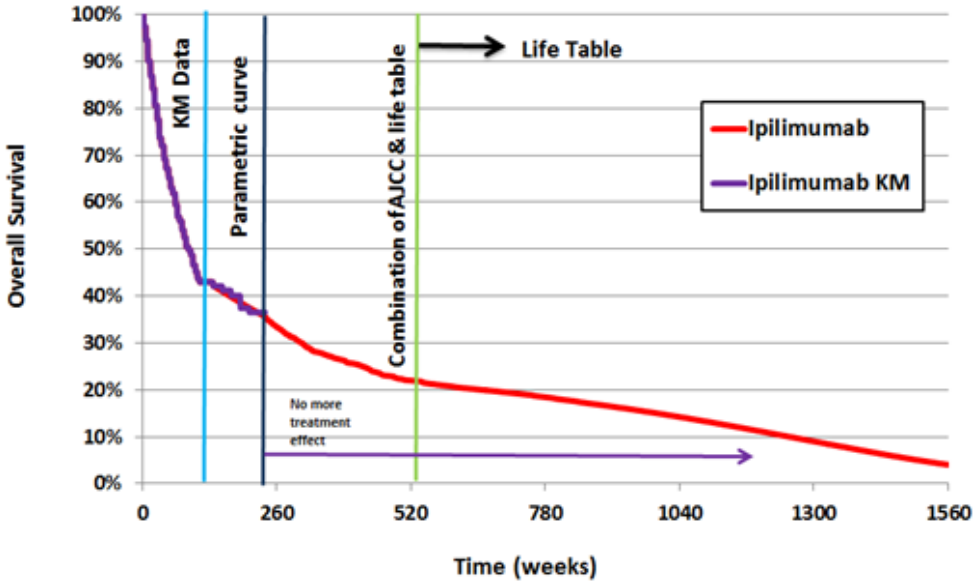
Figure 14 – Figure 16 show the results of the 3-part curve fit for overall survival used in the model

Figure 14 T-VEC overall survival 3-part curve fit



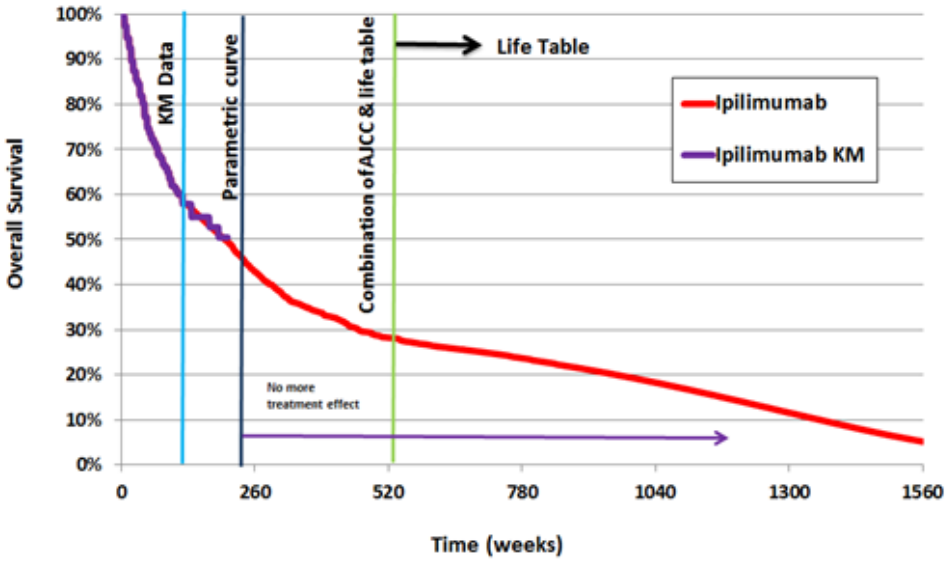
Source: company's submission, figure 5-13, page 137

Figure 15 Ipilimumab overall survival (based on modified Korn prediction model) 3-part curve fit



Source: company's submission, figure 5-14, page 137

Figure 16 Ipilimumab overall survival (based on 2-step Korn adjustment) 3-part curve fit



Source: company's submission, figure 5-15, page

5.7 The company obtained the utility values from NICE technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. The company included in the model adverse events of grade 3 or more with an incidence of 2% or more (see Table 5). Utility decrements because of adverse events were obtained from a time-trade-off study done by the company in the general population in the UK where respondents were asked to value different states associated with advanced melanoma (n=300). The company also used utility values from this study for the different states in the model and utility values sourced from the literature in sensitivity analyses. The utility values used in the company's model are shown in Table 6.

Table 5 Table Adverse events included in the model

Grade ≥3 AEs	T-VECa (%)	Ipilumumab (%)
Anaemia	-	3.1
Cellulitis	2.1	-
Colitis	-	5.3
Constipation	-	2.3
Diarrhoea	-	5.3
Dyspnea	-	3.9
Fatigue	-	6.9
Headache	-	2.3
Nausea	-	2.3
Vomiting	-	2.3
AE, adverse events; IPI, ipilimumab; T-VEC, talimogene laherparepvec Source company's submission, table 5-11, page 156		

Table 6 Summary of utility values in the model

State	Utility value: mean (standard error)	95% CI
Base-case values		
CR	0.77 (0.011)	0.75-0.79
PR	0.77 (0.011)	0.75-0.79
SD	0.77 (0.011)	0.75-0.79
PD	0.68 (0.084)	0.52-0.85
Disutilities associated with AEs		
Anaemia	0.09 (0.003)	0.083-0.097
Cellulitis	0.12 (0.005)	0.111-0.129
Colitis	0.26 (0.010)	0.241-0.280
Constipation	0.14 (0.005)	0.130-0.151
Diarrhoea	0.11 (0.004)	0.102-0.118
Dyspnea	0.11 (0.004)	0.102-0.118
Fatigue	0.05 (0.002)	0.046-0.054
Headache	0.16 (0.006)	0.148-0.172
Nausea	0.26 (0.010)	0.241-0.280
Vomiting	0.26 (0.010)	0.241-0.280
Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response, SD, stable disease Source adapted from company's submission, table 5-12, page 157		

5.8 The company included in the model data on healthcare resource use associated with treatment, disease progression, and palliative care. The

company did a survey and a costing study to estimate healthcare resource use associated with adopting T-VEC in the NHS. Costs and use of resources were also taken from different sources. The company estimated the cost of T-VEC based on individual patient-level data from OPTIM, calculating the mean number of vials per injection per day including wastage. Table 7 includes a summary of the costs included in the model (for further details on costs and use of resources see company's submission, table 5-22). Costs associated with adverse events were taken from NICE technology appraisal guidance on ipilimumab for previously untreated advanced melanoma and on ipilimumab for previously treated advanced (unresectable or metastatic) melanoma, and inflated to present year. The company assumed that the costs for managing nausea and vomiting were the same as for managing diarrhoea, and that the cost for managing anaemia was similar to the costs for managing fatigue. It also assumed that the cost of managing cellulitis was the same as for managing rash and that the cost for managing headache was the same as for managing pain. The cost of managing constipation and dyspnoea was assumed to be zero. The company stated that these assumptions were consistent with previous appraisals (see the company's submission, table 5-23 for further details on costs associated with adverse events).

Table 7 Summary of use of resources per state in the model

Health state	Cost	Frequency
Non-progressive disease		
Routine treatment	£86.52	Per cycle
Progressive disease		
On progression	£1,198.50	One-off
Best supportive care	£91.24	Per cycle
Palliative care	£192.03	Per cycle
Terminal care	£6,105.00	One-off
Source company's submission, table 5-21, page 171		

ERG comments

5.9 The ERG noted that the main comparator in the company model as the basis for assessing the incremental cost utility of T-VEC was not the comparator in the OPTiM trial (GM-CSF). The comparator in the company model was synthesised from ipilimumab data from two clinical trials. The reliability of this synthesised comparator was based upon six assumptions reliability of this synthesised comparator depends upon several assumptions. The ERG had the following concerns:

- The company's network focussed on ipilimumab as the main comparator whereas pembrolizumab may be a more relevant comparator

- Pooling ipilimumab data from the arms of two published clinical trials assumes that (a) dacarbazine and gp100 are both ineffective, (b) survival patterns are equivalent regardless of whether ipilimumab is administered as a first-line or as a subsequent line of therapy and (c) censoring occurs at a constant rate within each (arbitrary) time period. The ERG is not convinced that these assumptions can be substantiated

- The modified Korn model was used to correct for differences in patient characteristics between two ipilimumab trials and the OPTiM trial. The ERG considered that this model was not appropriate because it was developed using data from people with predominantly stage IV M1b and stage IV M1c disease, despite the OPTiM trial containing mostly people with stage IV M1a disease. In addition, the modified Korn model included an adjustment for elevated lactate dehydrogenase (LDH), which is not relevant for people with stage IIIB, stage IIIC or stage IV M1a disease, but had the effect of reducing the size of the coefficients associated with other adjustment factors (and improving the relative efficacy of T-VEC). Korn data are dominated by the most seriously affected patient groups (stage IV M1b and stage IV M1c) rather than by

stage IV M1a patients who are the only stage IV patients featured in the target subgroup of the OPTiM trial. Furthermore, in the OPTiM trial 54.7% of T-VEC patients had stage IIIB, stage IIIC or stage IV M1a disease compared with less than 20% in the ipilimumab trials

- The effectiveness of ipilimumab may vary significantly by stage of disease. The company has attempted to correct for this case-mix imbalance by using the two-step Korn model, which is a further application of the modified Korn model. This additional adjustment is likely to mean that the problems previously described are further compounded.

- The original Korn publication includes both PFS and OS models. The PFS model is different from the OS model. The ERG, therefore, suggests that the company's use of the same modified Korn model for both OS and PFS is inappropriate. The ERG therefore suggested is likely to lead to misrepresentation of estimated PFS trends for ipilimumab and substantial additional uncertainty in estimated model outcomes, which in turn will affect the balance between survival time spent in the PFS and progressed health states.

Company's base-case results and sensitivity analysis

5.10 The company submission presented the results from the cost-effectiveness analysis of T-VEC compared with ipilimumab, at their list prices (£1445 per vial for T-VEC; £3,750 per vial for ipilimumab), for people with advanced melanoma and non-visceral disease (that is, stage IIIB – IVM1a melanoma) using the modified Korn prediction model and the 2-stage Korn adjustment (see section 5.5). [redacted]. The results in the company's submission showed that T-VEC was associated with 1.34 additional quality-adjusted

life years (QALYs) and an additional cost of [redacted] compared with ipilimumab when using the modified Korn prediction model, leading to an incremental cost-effectiveness ratio of [redacted] per QALY gained. When using the 2-stage Korn adjustment, the results showed that T-VEC provided 0.35 additional QALYs with an additional cost of [redacted] compared with ipilimumab, leading to an ICER of [redacted] per QALY gained. Subsequently, the company [redacted] incorporated a revised list price of £1670 which had been agreed with the Department of Health (increased from £1445) [redacted]. The most relevant cost effectiveness results are those that compared T-VEC [redacted] and ipilimumab [redacted], the ICERs were [redacted] per QALY gained using the modified Korn method, and [redacted] per QALY gained using the two-step Korn method). [redacted]

5.11 The company's main submission compared the outcomes from the model with the outcomes from OPTIM for T-VEC, noting that these were similar, and suggested that the short-term and long-term outcomes from the model were valid for T-VEC. It also noted that the results are subject to uncertainty derived from the methods used to estimate the treatment effect of ipilimumab in people with advanced melanoma with non-visceral disease (see section 4.13) and stated that the outcomes from the model for ipilimumab were better than those observed in the clinical trials from ipilimumab.

5.12 The company did sensitivity analysis varying duration of treatment, response rates, administration costs, discount rates, utility values and cost of terminal care by 20%. The company suggested that the variable that had the highest effect on the ICER for T-VEC compared with ipilimumab was duration of treatment with T-VEC and ipilimumab when using the modified Korn prediction model and the 2-stage Korn adjustment.

5.13 The company did probabilistic sensitivity analyses to assess the uncertainty around the variables included in the model (based on the list price of £1,445 for T-VEC). The results (comparing the respective list prices of T-VEC and ipilimumab) showed that when using the modified Korn prediction model, T-VEC was associated with 1.24 additional QALYs and [redacted] additional cost compared with ipilimumab, leading to an ICER of [redacted] per QALY gained. When using the 2-stage Korn adjustment, the probabilistic results showed that [redacted]), as it cost [redacted]ipilimumab and provided 0.24 additional QALYs. The cost-effectiveness acceptability curves showed that there was a probability of approximately 98% of T-VEC being cost-effective compared with ipilimumab at a maximum acceptable ICER of £20,000 per QALY gained when using the modified Korn prediction model. When using the 2-stage Korn adjustment, this probability was of approximately 80%. Probabilistic sensitivity analysis that incorporated both the T-VEC PAS discount and the ipilimumab PAS discount was not done by the company (the company was not privy to discounts of competitors).

ERG comments

5.14 The ERG stated that company is to be complemented for their thorough approach to the problem of defining a credible ipilimumab comparator from the available trial data. However, the difficulties associated with pooling data from very different clinical trials, and then applying multiple case-mix corrections in an effort to standardise published outcomes to the very different T-VEC population in the OPTiM trial, demonstrate the substantial uncertainty associated with the methods used and therefore with the outcome estimates obtained (see sections 5.9 above and 5.5.1 of the ERG report). The ERG suggested that the derived ipilimumab survival trends were not reliable, and were inadequate for estimating the cost effectiveness of T-VEC in the specified patient population, that is, people with non-visceral metastatic melanoma.

Company scenarios

5.15 The company did several scenario analyses varying the assumptions in the model. The scenario which showed the biggest change in the ICER was that of using data on accelerated dosing from OPTIM and the extension study. For this scenario, the ICER for T-VEC compared with ipilimumab was [redacted] per QALY gained when using the modified Korn prediction model and [redacted] per QALY gained when using the 2-stage Korn adjustment (these ICERs were based on the list prices of T-VEC and ipilimumab). The company noted that accelerated dosing is not recommended in the anticipated marketing authorisation for T-VEC. The results in all other scenarios were similar to the base-case results (for further details see table 5-32, page 204 in the company's submission).

ERG exploratory analyses

5.16 The ERG noted that within the company model different methods were applied sequentially to estimate overall over a period of 30 years from randomisation into the OPTiM trial. The four phases that were estimated were:

- Phase 1a (weeks 1-177): direct use of results from K-M analysis of the OPTiM trial data
- Phase 1b (weeks 178-269): estimated OS based on an exponential projection model developed by the company (no details are provided in the CS)
- Phase 2 (weeks 270-520): estimated OS based on survival trends calculated from case-mix adjusted published analyses of a patient registry used in the development of the AJCC staging classification system
- Phase 3 (weeks 521-1560): estimated overall survival based on applying age/sex adjusted life table mortality rates.

The ERG commented that it is generally appropriate to use K-M analysis results directly in a model before using projection methods. However, in this case, the final analysis of the trial data (figure 4-6 of the company submission) had not been used in the model. The ERG carried out a curve-fitting exercise to re-analyse the final data cut (requested during the clarification process). The ERG found that a 2-part exponential model closely followed the trial overall survival data from 9 months (~270 weeks) until the last recorded death at 47 months (~1400 weeks).

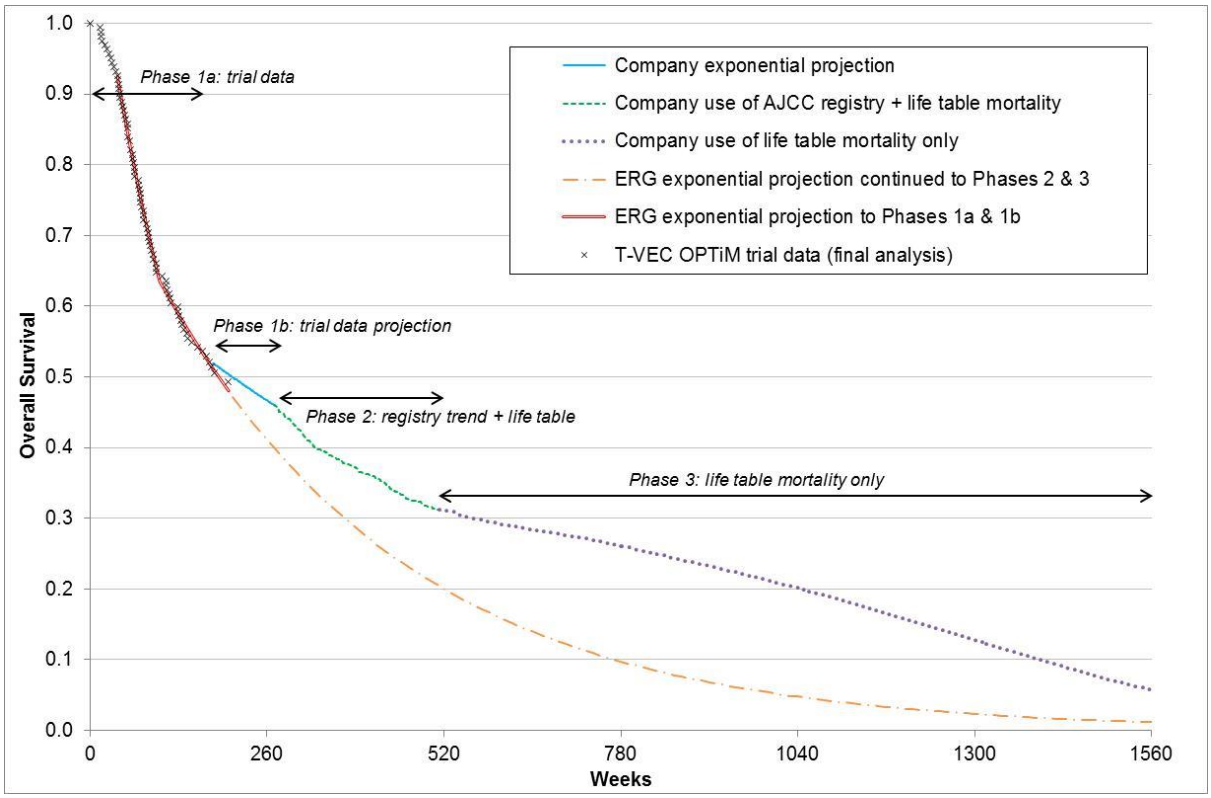


Figure 16. Company long-term T-VEC overall survival projection compared to ERG simple exponential alternative projection (see figure 8, page 89 of the ERG report).

5.17 The ERG highlighted that the company model exponential trend (Phase 1b in figure 16) deviated markedly from the final recorded trial data and leads to a clear separation from the exponential trend identified by the ERG. This resulted in a more advantageous overall survival estimate for

T-VEC compared to the long-term projection resulting from the fitted ERG curve. The ERG's projections suggested that the company estimate for the mean overall survival of those treated with T-VEC may have been overstated by 49% to 59%. This could have a substantial effect on the model estimates of QALYs gained from treatment with T-VEC compared to any comparator, leading to sizeable increases in the size of estimated ICERs.

5.18 In the second phase of modelling the overall survival, the company used the published results of the analyses of patient registry data on which the AJCC staging classification was based, with the addition of UK life table information. The ERG commented that:

- the AJCC trends only provided results for a maximum of 10 years from the date of diagnosis for patients with stage I to stage III disease, and from the recorded time of first distant metastases for patients with stage IV disease. The ERG highlighted that this meant the estimates used in the company model mixed patients at very different times in their disease career, starting from 0 to more than 20 years after first diagnosis

- the application of the data on which the AJCC analysis was performed (these data were gathered before the current era of novel immunological treatments) to model the survival data in the OPTiM trial implied that T-VEC had little or no continuing benefit after 5 years

- there was no clinical justification to support such a sudden change in the long-term mortality rate at the junction between Phase 1b and Phase 2 in the company model where there was an increase in the mortality rate after exactly 270 weeks (62.1 months).

- For phase 3 of the overall survival projection, it was not aware of any evidence that the remaining cohort of long-term survivors is at the same mortality risk as the general population.

5.19 The ERG identified a number of other issues relating to the model which all increased the ICER by a small amount. Of note, the ERG commented that the health state utility values obtained from the commissioned study had greater face validity than those used in the base case analysis, which were from the appraisal of dabrafenib (TA321) in which there was no difference in utility with complete response, partial response and stable disease. The ERG applied the commissioned study utility estimates which reduced the number of incremental QALYs gained.

5.20 Because of the issues highlighted by the ERG, it did not consider that any estimates of the cost effectiveness of T-VEC compared with ipilimumab in patients with non-visceral metastatic disease were reliable. The ERG suggested that using different assumptions, widely differing estimated ICERs could be obtained. For example, T-VEC appeared to be dominant compared with ipilimumab (better outcomes at lower cost) in the modified Korn model to being dominated by ipilimumab (poorer outcomes at higher cost) in the 2-step Korn model, so that quoting any specific ICERs would be unreliable. However, the ERG attempted to attribute a broad indication of the significance of the issues identified by the ERG.

- The company base case analysis used the list price for ipilimumab and the proposed list price for T-VEC. Thus the current PAS price for ipilimumab was not applied. Results from the company model suggested that the estimated cost effectiveness of T-VEC was substantially worsened when using the reduced ipilimumab PAS price.

- Taken separately, the ERG approach to estimating OS and PFS had contrary effects on the estimated cost effectiveness: the revised overall survival estimate appeared to improve the cost effectiveness of T-VEC, whereas the revised PFS estimate worsened it.

- All of the other issues identified when considered individually had a very small impact on the position of T-VEC, generally increasing the size of the estimated ICER per QALY gained.

- When the PAS for ipilimumab was applied alongside the ERG's overall survival and progression-free survival estimates, the ICER per QALY gained was increased to a value far beyond the range normally considered acceptable.

- The cost effectiveness of T-VEC compared to ipilimumab varies from dominating (more effective at less cost in the modified Korn model) to being dominated (less effective at greater cost in the two-step Korn model).

Innovation

5.21 The company included the following justifications for considering T-VEC to be innovative:

- It is a first-in-class oncolytic immunotherapy with a dual mechanism of action that produces local tumour control and systemic anti-tumour immune responses

- It is administered by intralesional injection

- It is the only treatment approved specifically in patients with regionally or distantly metastatic melanoma with no visceral disease (stage IIIB-IVM1a disease) and has shown a major clinical advancement in treatment for this population

- It is associated with fewer treatment-related grade 3 and 4 adverse events compared with other existing treatment options for advanced melanoma.

6 Equality issues

6.1 No equality issues were raised during scoping consultation, at the scoping workshop or in the evidence submitted.

7 Authors

Pilar Pinilla Dominguez and Christian Griffiths

Technical Leads

Eleanor Donegan

Technical Adviser

with input from the Lead Team (Dr John Watkins, Ellen Rule and Pamela Rees)

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002771/WC500201082.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talimogene laherparepvec for treating metastatic melanoma

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of talimogene laherparepvec within its marketing authorisation for treating metastatic melanoma.

Background

Melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, at presentation, around 10% of melanomas have spread to nearby lymph nodes (stage III) or to other parts of the body (stage IV). It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at increased risk.

There were 11,281 new diagnoses of melanoma and 1781 deaths registered in England in 2012. In the UK, more than one-third of people diagnosed with melanoma are aged less than 55 years. Approximately 20–73% of people with stage III melanoma (including 20–34% of people with stage IIIc) and 5–22% of those with stage IV will live longer than 5 years, with survival rates being slightly higher in women than in men.

Approximately 50% of melanomas harbour activating BRAF mutations, and over 90% of these are BRAF V600 mutations. Diagnostic tests can be used to detect the BRAF mutation, including the cobas test, generic PCR sequencing tests and other validated BRAF mutation tests.

The management of advanced melanoma is rapidly evolving, with several ongoing clinical trials, and there is uncertainty about how these treatments will be sequenced in future. Treatment for advanced, unresectable melanoma is often based upon the person's BRAF mutation status and their previous treatment history.

NICE Technology Appraisal (TA) 319 recommends ipilimumab as a treatment option for adults with previously untreated unresectable or metastatic melanoma and TA268 recommends ipilimumab as a treatment option for previously treated disease. For people with a BRAF V600 mutation, TA269 and TA321 recommend the BRAF inhibitors vemurafenib and dabrafenib as treatment options. Ipilimumab, vemurafenib and dabrafenib are only recommended if the respective companies provide the drugs at the discount agreed in the patient access schemes. Dacarbazine and supportive care may also be considered when ipilimumab or BRAF inhibitors are unsuitable or have already been tried.

The technology

Talimogene laherparepvec (Brand name unknown, Amgen) is an oncolytic immunotherapy designed to selectively replicate in tumour tissue and to initiate a systemic anti-tumour immune response. It expresses granulocyte-macrophage colony-stimulating factor (GM-CSF), a white blood cell growth factor, which can help to activate the immune system. The aim of this combination of actions is to initiate a systemic anti-tumour immune response that targets tumour cells throughout the body. It is administered by intratumoral injection.

Talimogene laherparepvec does not have a marketing authorisation in the UK for treating metastatic melanoma. It has been studied in a clinical trial compared with subcutaneously administered GM-CSF in people with unresected stage IIIb – IV melanoma.

Intervention(s)	Talimogene laherparepvec
Population(s)	Adults with advanced (unresectable or metastatic) melanoma
Comparators	• ipilimumab • vemurafenib (for people with BRAF V600 mutation positive disease) • dabrafenib (for people with BRAF V600 mutation positive disease)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • time to treatment failure • durable response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal

	Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows, consideration will be given to subgroups based on volume of disease and distribution of disease. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE pathways	Related Technology Appraisals: Technology Appraisal 268, Dec 2012, 'Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'. Static list. Technology Appraisal 269, Dec 2012, 'Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.' Static list. Technology Appraisal 319, Jul 2014, 'Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma'. Review proposal date Jun 2017. Technology Appraisal 321, Oct 2014, Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Review proposal date Oct 2017. Ongoing appraisals: Technology Appraisal in preparation, ID661, 'Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma'**.** Earliest anticipated date of publication Aug 2016. Technology Appraisal in preparation, ID760, 'Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab'. Earliest anticipated date of publication Dec 2015. Technology Appraisal in preparation, ID801, 'Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab'**.** Earliest anticipated date of publication Jan 2016. Technology Appraisal in preparation, ID815,

	'Cobimetinib in combination with vemurafenib for treating previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma'. Earliest anticipated date of publication TBD. Technology Appraisal in preparation, ID845, 'Nivolumab for treating advanced (unresectable or metastatic) melanoma'. Earliest anticipated date of publication TBD. Related Guidelines: Clinical Guideline in preparation, 'Melanoma: assessment and management of melanoma'. Earliest anticipated date of publication July 2015. Related Interventional Procedures: Interventional procedure guidance 446, Mar 2013, 'Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma'. Review proposal date TBC. Interventional Procedure Guidance in preparation, 'Electrochemotherapy for the treatment of malignant melanoma (GID-IP1041)'. Earliest anticipated date of publication TBC. Related Public Health Guidance/Guidelines: Public health guidance 32, Skin cancer prevention: information, resources and environmental changes January 2011. Part review in progress; next review date Apr 2017. Related NICE Pathways: Skin cancer NICE Pathway, published July 2014Other guidance: Cancer Service Guidance CSGSTIM, May 2010, 'Improving outcomes for people with skin tumours including melanoma'.
Related National Policy	NHS England, 2013/14, NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a. NHS England, 2013/14, NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a. National Cancer Peer Review Programme, 2013, Manual for Cancer Services: Skin Measures. National Service Frameworks, Cancer Department of Health, 2013, NHS Outcomes

	Framework 2014-2015. Domains 1, 2, 4 and 5. Department of Health, 2011, Improving outcomes: a strategy for cancer Department of Health, 2009, Cancer commissioning guidance Department of Health, 2007, Cancer reform strategy

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company(ies) • Amgen (talimogene laherparepvec) Patient/carer groups • Black Health Agency • British Skin Foundation • Cancer Black Care • Cancer Equality • Cancer 52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Melanoma UK • Muslim Council of Britain • OcuMel UK • Rarer Cancers Foundation • Skcin - Karen Clifford Skin Cancer Charity • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Professional groups • Association of Anaesthetists • Association of Cancer Physicians • Association of Surgeons of Great Britain and Ireland • British Association of Dermatologists • British Association of Skin Cancer Specialist Nurses • British Association of Surgical Oncology	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Bristol-Myers Squibb Pharmaceutical (ipilimumab) • Novartis (dabrafenib) • Roche Products (vemurafenib) Relevant research groups • British Society for Dermatological Surgery • Cochrane Skin Group • Institute of Cancer Research • MRC Clinical Trials Unit • Myfanwy Townsend Melanoma Research Fund • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research

Consultees	**Commentators (no right to submit or appeal)**
• British Dermatological Nursing Group • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • Cancer Research UK • Melanoma Focus • Primary Care Dermatology Society • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Nene CCG • NHS Warrington CCG • Welsh Government	• Skin Cancer Research Fund • Skin Research Centre • Skin Treatment & Research Trust <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that manufactures the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that manufactures the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that manufacturer comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma

Company evidence submission

Amgen Limited

November, 2015

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

Contents

Appendices

Number	Title
1.1	European public assessment report, SmPC/IFU, scientific discussion or drafts
1.2	Clinical, economic and PRO systematic reviews
1.3	Clinical effectiveness results of the relevant randomised controlled trials – ITT population (primary analysis)
1.4	NMA evidence base – Summary of methods, baseline characteristics and results for RCTs (excluding OPTiM)
1.5	Quality assessment for cost-effectiveness studies
1.6	List of parameters used in the economic model
1.7	Utility study for advanced melanoma
1.8	T-VEC administration cost study
1.9	Checklist for model validation
1.10	Modified Mantel-Haenszel method to pool survival curves

List of tables

List of figures

Abbreviations

AE	Adverse event
ANC	Absolute neutrophil count
BMS	Bristol Myers Squibb
CG	Clinical guideline
CR	Complete response
DRR	Durable response rate
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GM-CSF	Granulocyte-macrophage colony-stimulating factor
gp100	glycoprotein 100
HR	Hazard ratio
HRQoL	Health-related quality of life
HSV-1	Herpes simplex virus type-1
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IVRS	Interactive voice response system
KOL	Key opinion leader
LDH	lactate dehydrogenase
NMA	Network meta analysis
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression free survival
PFU	Plaque forming units
PR	Partial response
PS	Performance status
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Stable disease
SLR	Systematic literature review
TA	Technology apparaisal
TTF	Time to treatment failure
T-VEC	Talimogene laherparepvec
UV	Ultraviolet

1 Executive summary

Introduction

Melanoma is a rare but serious skin cancer that can rapidly infiltrate deep, vascular skin layers, and can commonly metastasise very early. In patients with unresectable metastatic melanoma (stage IIIB-IV), overall survival (OS) is poor, regardless of stage of disease: Even in non-visceral metastatic disease (stage IIIB-IVM1a), patients have a short life expectancy, with a median OS of less than 24 months. Although the treatment paradigm in melanoma continues to expand, with recently licensed treatments rapidly becoming the new standard of care, current treatments show a lack of durable response, low complete response rates and a toxicity profile that may not be well tolerated. For patients with non-visceral metastatic disease, the evidence base for currently used therapies is minimal; with no evidence to show that treatments can delay progression to visceral disease. Therefore for these patients there remains an unmet need for effective, well tolerated therapies that provide both high and durable response rates and delay/prevent progression to visceral disease, in order to deliver long term survival benefit for patients with this serious, life-threatening disease.

Talimogene laherparepvec (T-VEC) has been recognised by the EMA as an innovative first-in-class advanced therapy medicinal product (ATMP), derived from a virus and has been awarded CHMP positive opinion for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. T-VEC is a novel oncolytic immunotherapy with a unique dual mechanism of action that produces local tumour control as well as systemic anti-tumour immune responses; it is also the only therapy to be administered intralesionally. In a randomised open-label phase III trial, T-VEC was compared with granulocyte-macrophage colony-stimulating factor (GM-CSF), an unlicensed but potentially immunologically active agent, in patients with unresectable stage IIIB to IV melanoma. In an analysis of patients with non-visceral metastatic disease (stage IIIB-IVM1a), T-VEC demonstrated a clinically significant and meaningful improvement in OS, in addition to high and durable rates of response (CR and DRR) and a highly favourable safety profile.

Ipilimumab, dabrafenib and vemurafenib are all relevant comparators defined in the decision problem. Ipilimumab, like T-VEC is indicated for all patients regardless of BRAF status, whilst BRAF inhibitors are only approved for those 48% of patients with the BRAF V600 mutation. In clinical practice patients with non-visceral metastatic disease (stage IIIB-IVM1a) are routinely treated with immunotherapies rather than BRAF inhibitors, except where there is evidence of rapidly progressing disease and high disease burden (NICE guidance TA319/TA321 and expert opinion). Ipilimumab is therefore considered to be the primary comparator in the submission. Due to limitations of the evidence base, indirect comparisons of T-VEC versus ipilimumab were conducted by predicting survival outcomes for ipilimumab, using two methods based on the Korn algorithm; the modified Korn method resulted in a favourable OS for T-VEC, whilst the two-step method reduced the difference, but was still favourable for T-VEC.

The cost-effectiveness analyses presented in this submission are based on the anticipated list price of T-VEC. Amgen have proposed a Patient Access Scheme (PAS) to the Department of Health which is undergoing consideration by the Patient Access Scheme Liaison Unit. When the PAS is incorporated into the cost-effectiveness analyses, T-VEC remains a cost-effective option versus the primary comparator, ipilimumab, even when using the best estimate of survival for ipilimumab for the treatment of patients with non-visceral metastatic disease (stage IIIB-IVM1a).

1.1 Statement of the decision problem

An overview of the decision problem is provided in Table 1-1.

Table 1-1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the final NICE scope
Population	Adults with stage IIIB-IV melanoma	Adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (disease stages IIIB–IVM1a) described within this submission as non-visceral metastatic disease	In accordance with anticipated license
Intervention	Talimogene laherparepvec	Talimogene laherparepvec	N/A
Comparator (s)	-Ipilimumab -Vemurafenib (for people with BRAF V600 mutation positive disease) -Dabrafenib (for people with BRAF V600 mutation positive disease)	Ipilimumab	For patients with non-visceral metastatic disease (stage IIIB-IVM1a), ipiliumumab is considered to be the primary comparator in the submission since BRAF inhibitors are often reserved for those patients with rapidly progressing disease and high disease burden. Further, the assessment of comparative effectiveness using the Korn algorithm presents significant challenges with respect to the BRAF inhibitors
Outcomes	-Overall survival -Progression-free survival -Time to treatment failure -Response rate -Adverse effects of treatment -Health-related quality of life	Overall survival -Progression-free survival -Time to treatment failure -Response rate (durable response rate and overall response rate) -Adverse effects of treatment -Health-related quality of life	N/A
Economic analysis	In accordance with the NICE reference case	Cost effectiveness of treatments is expressed in	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the final NICE scope
	which stipulates: The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	terms of incremental cost per quality-adjusted life-year A lifetime time horizon reflecting any differences in costs or outcomes between the technologies being compared has been modelled Costs are considered from an NHS and Personal Social Services perspective	
Subgroups to be considered	None.	None.	N/A
Special considerations including issues related to equity or equality	None	None	N/A
ITT, intent-to-treat; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; QALY, quality-adjusted life year			

1.2 Description of the technology being appraised

The technology intended for appraisal in this submission is described in Table 1-2.

Table 1-2: Description of technology being appraised

UK approved name [brand name]	Talimogene laherparepvec (T-VEC) [Imlygic]
Marketing authorisation/CE mark status	T-VEC does not currently have UK marketing authorisation: an application was made to the EMA in September 2014 via the centralised process. The EMA recognised T-VEC as an innovative first-in-class advanced therapy medicinal product (ATMP) derived from a virus and the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending that Imlygic™ (talimogene laherparepvec) be granted approval 'for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease' on 23 October 2015. Marketing authorisation for T-VEC in the EU is expected in December 2015. The anticipated date of availability in the UK is January 2016

Indications and any restriction(s) as described in the summary of product characteristics	T-VEC is indicated for the treatment of adults with unresectable melanoma that regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease
Method of administration and dosage	T-VEC is administered via intralesional injection up to a maximum of 4 mL per treatment The initial recommended dose is at a concentration of 10^6 (1 million) PFU/mL. The second dose is 3 weeks later, and subsequent doses are biweekly at a concentration of 10^8 (100 million) PFU/mL.
EMA, European Medicines Agency; EU, European Union; PFU, plaque forming units; T-VEC, talimogene laherparepvec	

1.3 Summary of the clinical effectiveness and safety/tolerability analysis

Summary of evidence and methods

T-VEC RCT and non-RCT evidence

A systematic literature review (SLR) identified a total of 59 RCTs evaluating treatments for stage IIIB-IV metastatic melanoma. Only one RCT evaluated T-VEC: OPTiM was a phase III, randomised, active-controlled, multicentre study comparing T-VEC and GM-CSF, in patients with unresectable, stage IIIB/C and stage IV malignant melanoma (N=436). GM-CSF was used as a comparator within the study because it was a potentially immunologically active agent however it is not a defined comparator within the decision problem. An exploratory subgroup analysis of patients with stage IIIB-IVM1a disease (which aligned with the proposed license for T-VEC in non-visceral metastatic disease) was conducted. This consisted of 57% of the ITT population (N= 249). There was no head-to-head RCT evidence comparing T-VEC with any of the relevant comparators defined in the decision problem.

A systematic review of non-RCT evidence identified 178 studies, of which one evaluated T-VEC: Study 002/03 was a single arm phase II study in patients with stage IIIC/IV malignant melanoma, involving 50 patients.

Evidence and methods for indirect comparisons

Network meta-analysis Feasibility Assessment

In the absence of relevant head-to-head RCT evidence, efforts were made to conduct a NMA to evaluate T-VEC versus relevant comparators. The broad evidence base identified by the SLR showed that the OPTiM study was an isolated trial, with no common comparator linking to other published trials or publicly available data. In order to present and describe the key clinical evidence relevant to the decision problem, further inclusion/exclusion criteria were applied to identify those phase III RCTs which evaluated interventions/comparators defined in the scope, as monotherapy, for the treatment of patients with stage IIIB-IV melanoma. Ten phase III RCTs (including OPTiM) were identified; T-VEC (1), ipilimumab (4), vemurafenib (3) and dabrafenib (2) as a monotherapy. All ten RCTs reported efficacy for the broad population of patients with stage III-IV metastatic melanoma. However only OPTiM reported efficacy for the stage IIIB-IV1a population, which comprised 57% of patients, compared with only 11%-17%, for ipilimumab, 18%-23% with vemurafenib and 16% and 18% for dabrafenib. Given the challenges of both a disconnected network and the

significant differences in disease stage of the patient populations, it was concluded that a NMA was not feasible.

Alternative methods of indirect comparisons of clinical effectiveness
An evaluation of alternative methods for comparing survival outcomes for T-VEC versus comparators was conducted. This included methods that use individual patient level data to adjust the outcomes of interventions to match comparator populations, and those that use prognostic equations to adjust comparator populations. The methodology based on adjusting the comparator populations using the Korn prognostic equation was considered the most suitable approach, as it captures the impact of key prognostic variables, importantly the presence of visceral disease. Two approaches with respect to the Korn adjustment were considered; the modified Korn method which includes a key fifth prognostic factor LDH, and the two-step Korn method which uses the modified Korn equation and includes a potential treatment effect between ipilimumab and stage of disease, but on the basis of highly uncertain evidence. The modified Korn method assumes the absence of an interaction effect for ipilimumab in the T-VEC licensed population (best case) and the two-step Korn method assumes the full interaction effect for ipilimumab based on uncertain clinical evidence (worst case).

Ipilimumab was deemed to be the primary comparator for this submission and both approaches with respect to the Korn adjustment were applied. In addition, the Korn methodology was not considered suitable to adjust the survival curves of vemurafenib and dabrafenib, since the Korn algorithm, did not include BRAF status as a baseline prognostic variable (a critical prognostic gene for the BRAF inhibitors).

The evidence used in the application of the Korn methodology included those RCTs which evaluated T-VEC and ipilimumab and reported OS data, and used the pivotal RCT for T-VEC (OPTiM) and the 2 pivotal RCTs for ipilimumab.

Results of OPTiM RCT: T-VEC versus GM-CSF

Efficacy

In the ITT analysis (in patients with unresectable stage IIIB/C and stage IV malignant melanoma), the OPTiM study met its primary endpoint demonstrating that T-VEC resulted in a statistically significant improvement in durable response rate (DRR) compared to GM-CSF (16.3% vs 2.1%, p<0.0001).

In the analysis of patients with stage IIIB-IVM1a malignant melanoma (N=249), DRR was higher in patients treated with T-VEC compared with the GM-CSF (25.2% vs 1.2%; p<0.0001). Evaluation of response rates showed a CR rate of 16.6% in the T-VEC arm compared to 0.0% in the GM-CSF arm (p < 0.001); with 1 in 6 patients treated with T-VEC achieved CR in this population. An ORR (CR + PR) of 40.5% was achieved in the T-VEC arm compared to 2.3% in the GM CSF arm (p < 0.0001). The ORR results achieved with T-VEC were generally durable; with the durable response rate (DRR) 25.2% in the T-VEC arm versus 1.2% in the GM-CSF arm (odds ratio [OR] was 28.6 [95% CI: 3.9, 211.5]; p < 0.0001).

In the analysis of patients with stage IIIB-IVM1a malignant melanoma, T-VEC also produced a clinically significant and meaningful median OS gain of 25.3 months versus GM-CSF (46.8 vs 21.5 months, p=0.0008 in the final data cut). Among patients who achieved a DR, the survival rate at at 4 years was 87%. In addition to improved OS, achieving DR was associated with reduced risk of initiating subsequent systemic therapy: HR (DR vs no DR) = 0.33 (95% CI: 0.17-0.65), P=0.0007 and patients with a DR had a higher quality of life improvement rates vs patients with no DR: odds ratio (DR vs no DR) = 2.8 (95% CI: 1.1-7.0), P=0.0247.

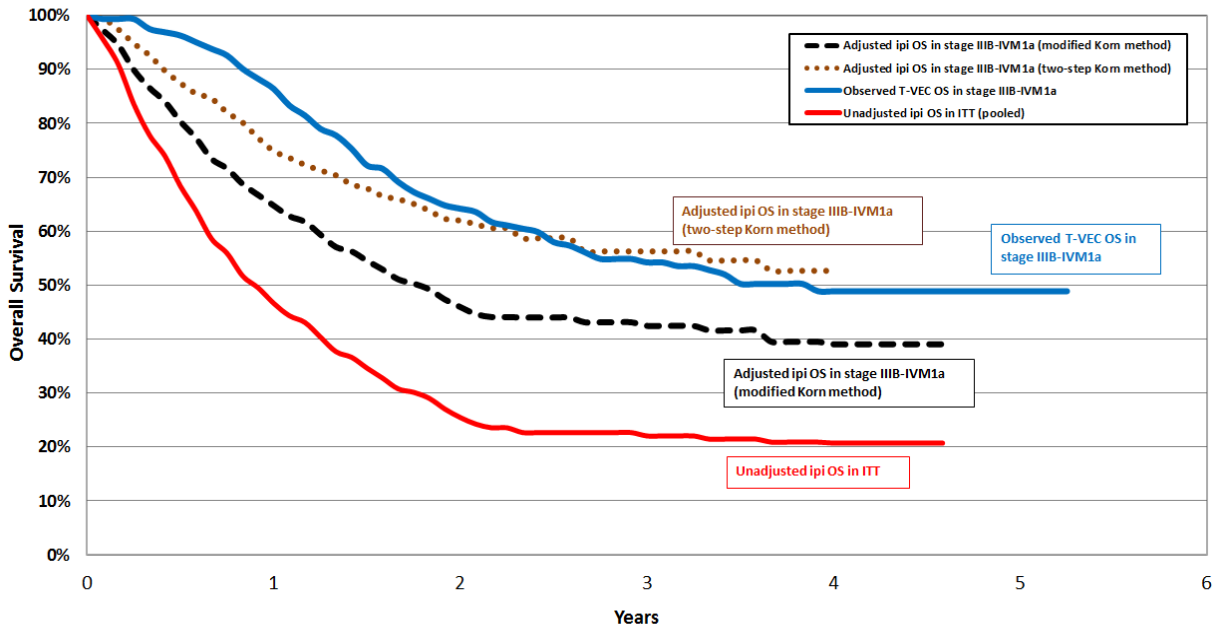
Safety

Treatment related adverse events (AEs) with T-VEC were generally mild and reversible. Few patients discontinued because of toxicity. The most common treatment-related AEs were flu-like symptoms (including fatigue, chills, and pyrexia). There were no treatment-related deaths. There was only one grade 3 or 4 AE (treatment emergent) occurring in >2% of T-VEC–treated patients (cellulitis, 2.1%). This toxicity profile compares favourably to the other treatment options, especially ipilimumab, which is commonly associated with immune-related AEs (particularly diarrhoea and colitis), which can be fatal.

Results of indirect comparisons of survival outcomes: T-VEC versus ipilimumab

The modified Korn method was used to predict survival for ipilimumab, assuming the baseline characteristics of the T-VEC licensed trial population (based on prognostic variables of gender, ECOG performance status, visceral status, brain metastases and high lactate dehydrogenase) and assigning no interaction effect between ipilimumab treatment the stage IIIB-IVM1a disease population. Figure 1-1 illustrates the observed and Korn adjusted (modified Korn method and two-step Korn method) OS for ipilimumab and the observed survival for T-VEC. Using the modified Korn method, there was a predicted median overall survival gain of approximately two years for T-VEC in the stage IIIB-IVM1a disease population. Using the two-step Korn method, which assumed a potential interaction effect and assigned a full interaction effect (HR=0.47) based on highly uncertain clinical evidence of subgroup data in a very small proportion of patients), T-VEC was at least comparable to ipilimumab.

Figure 1-1: Observed and Korn-adjusted survival curves for ipilimumab and observed survival curve for T-VEC



The adjustment using the the Korn methodology was only applied to ipilimumab as ipilimumab was deemed to be the main relevant clinical comparator.In addition, given the importance of the prognostic gene BRAFV600 and the issue around the omission of this key variable in the Korn methodology, there are significant challenges in applying the Korn methodology to the BRAF inhibitors. It is noteworthy that previous NICE appraisals have assumed equivalence of efficacy between ipilimumab, dabrafenib and vemurafenib (TA319; TA321)[1,2].

Strengths and limitations of the evidence base

T-VEC was studied in a large, phase III, prospective, randomised clinical trial that included a large group of patients with non-visceral metastatic disease (stage IIIB-IVM1a), in which existing therapies have not been extensively studied. The results from the OPTiM study show that T-VEC consistently demonstrated clinically significant improvements in efficacy measures across primary and secondary endpoints. T-VEC also demonstrated improvement in durable and complete responses, and clinically significant and meaningful survival benefit. Assessment of comparative effectiveness for T-VEC versus the defined comparators using a NMA was rendered unfeasible by a disconnected network of evidence and the heterogeneity of the RCT patient population with regards metastatic disease stage (there was minimal data on effectiveness for comparators in the T-VEC-licensed population). The modified Korn and two-step Korn approaches were used in an attempt to overcome these limitations. The modified Korn analysis assumes the absence of a potential interaction effect between ipilimumab treatment and stage IIIB-IVM1a disease, and may be an underestimate of the treatment effect for ipilimumab. The two-step Korn analysis, assumed an interaction effect between ipilimumab treatment and the stage of metastatic disease. However, the magnitude of the interaction effect was based on the best possible estimate of effect (HR 0.47) for

ipilimumab based on a subgroup analysis, subject to considerable uncertainty, where stage IIIB-IVM1a patients formed only 10.7% of the ITT population.

Summary of clinical evidence

The OPTiM trial showed that, in the licensed population (patients with stage IIIB-IVM1a disease), T-VEC resulted in a high and durable rate of response, with a median OS gain of 25.3 months versus GM-CSF (a potentially immunologically active agent), combined with a favourable safety profile. In order to overcome the severe limitations of the evidence base for comparative effectiveness, two methods were used to predict survival outcomes for the primary comparator ipilimumab, assuming the baseline characteristics of the T-VEC licensed stage IIIB-IVM1a trial population. The modified Korn adjustment which accounts for prognostic variability by stage of disease and assumes an absence of an interaction effect (best case scenario), and the two-step Korn adjustment which bestowed a full treatment interaction effect, based on highly uncertain clinical evidence (worst case scenario). Even in the worst case scenario, T-VEC is no less effective compared to ipilimumab.

On the basis of these analyses, it is plausible that in the non-visceral metastatic disease population, T-VEC provides an improvement in survival over ipilimumab and at worse, is comparably effective. This, combined with a very favourable safety profile, demonstrates that T-VEC is a valuable treatment option for patients with non-visceral metastatic disease (stage IIIB, IIIC and IVM1a), for whom none of the comparators has evidence of efficacy.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of T-VEC in its licensed population was evaluated versus ipilimumab. A de novo three-state partitioned cost-effectiveness model that considered PFS, post-progression and death, in line with previous HTAs concerning metastatic melanoma was developed. The model projected survival outcomes, OS and PFS, to estimate patients health-related quality of life (HRQoL) and costs over a lifetime horizon. Quality-adjusted life years (QALYs) were estimated by using progression-based utilities derived from EQ-5D data, in line with a recent NICE submission in melanoma[1]. The model evaluated T-VEC in both previously treated and untreated patient population.

Cost-effectiveness of T-VEC was evaluated versus the primary comparator ipilimumab. The overall survival for T-VEC was estimated using a piecewise curve fitting approach; first Kaplan Meier data based on the OPTiM trial was used up to a cut-point, second regression models were applied until end of observed trial period and third long-term registry data used from end of observed trial till end of model time horizon. For progression free survival, regression models were applied to project survival across all periods. The same approach with respect to curve fitting was applied to ipilimumab.

The base case uses both of the two alternative approaches for predicting survival; the modified Korn method which assumes the absence of an interaction effect for ipilimumab in the T-VEC licensed population (best case) and the two-step Korn method which assumes the full interaction effect for ipilimumab based on uncertain clinical evidence (worst case). The likely ICER is expected to lie somewhere between the best and the worst case approaches.

When comparing T-VEC with ipilimumab at anticipated and current NHS list prices, respectively, T-VEC resulted in 1.34 additional QALYs and an additional cost of [redacted] when using the modified Korn method. When using the two-step Korn method, T-VEC resulted in 0.35 additional QALYs with an additional cost of [redacted]. T-VEC remains cost-effective when compared with ipilimumab at the usual ICER thresholds accepted by NICE using both the modified Korn method and the two-step Korn method. Amgen have also proposed a Patient Access Scheme (PAS) to the Department of Health which is undergoing consideration by the Patient Access Scheme Liaison Unit, but results incorporating the proposed PAS have not been presented in the submission.

In the analyses using the modified Korn method and comparing T-VEC with ipilimumab in a range of potential PAS discounts for ipilimumab, T-VEC remained cost-effective (below a threshold of £30,000 per QALY) when the discount for ipilimumab was increased up to 55%. For the two-step Korn method, the ICER remained below £30,000 per QALY when the discount for ipilimumab was increased up to 10%.

Probabilistic sensitivity analyses demonstrate that there is a more than 90% chance of T-VEC being cost-effective compared to ipilimumab at both the £20,000 per QALY and £30,000 per QALY thresholds. When using the two-step Korn adjustment, there is a more than 80% chance of T-VEC being cost-effective compared to ipilimumab at both QALY thresholds.

An overview of the results for incremental cost-effectiveness of T-VEC versus ipilimumab is shown in Table 1-3.

Table 1-3 Incremental cost-effectiveness results - based on anticipated list price of T-VEC and NHS list price of Ipilimumab

Technology (and comparators)	Total costs £	Total life years	Total QALYs	Incremental costs £	Incremental life years	Incremental QALYs	ICER (£) incremental QALYS
Modified Korn							
Ipilimumab	98,219	4.90	3.57	-	-	-	-
T-VEC	[redacted]	6.66	4.91	[redacted]	1.76	1.34	[redacted]
two-step Korn							
Ipilimumab	96,035	6.16	4.61	-	-	-	-
T-VEC	[redacted]	6.66	4.95	[redacted]	0.50	0.35	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

Conclusion

The cost-effectiveness analyses presented in this submission are based on the anticipated list price for T-VEC and the NHS list price for ipilimumab. T-VEC is a cost-effective option versus the primary comparator, ipilimumab, even when using the most conservative estimate for T-VEC (based on the two-step Korn) for the treatment of patients with non-visceral metastatic disease (stage IIIB-IVM1a). Amgen have proposed a PAS to the Department of Health which is undergoing consideration by the Patient Access Scheme Liaison Unit. There

is a plausible chance that T-VEC is more effective than ipilimumab in this specific population and at worse no less effective. The proposed PAS is a response to the uncertainties in estimating a treatment interaction effect for ipilimumuab in the T-VEC licensed population and mitigates any risk to the NHS. Although these uncertainties relate more to limitations of the evidence base of ipilimumab in the expected licensed population for T-VEC.

2 The technology

2.1 Description of the technology

Brand name

Imlygic®

Approved name

Talimogene laherparepvec (T-VEC)

Therapeutic class

Oncolytic immunotherapy

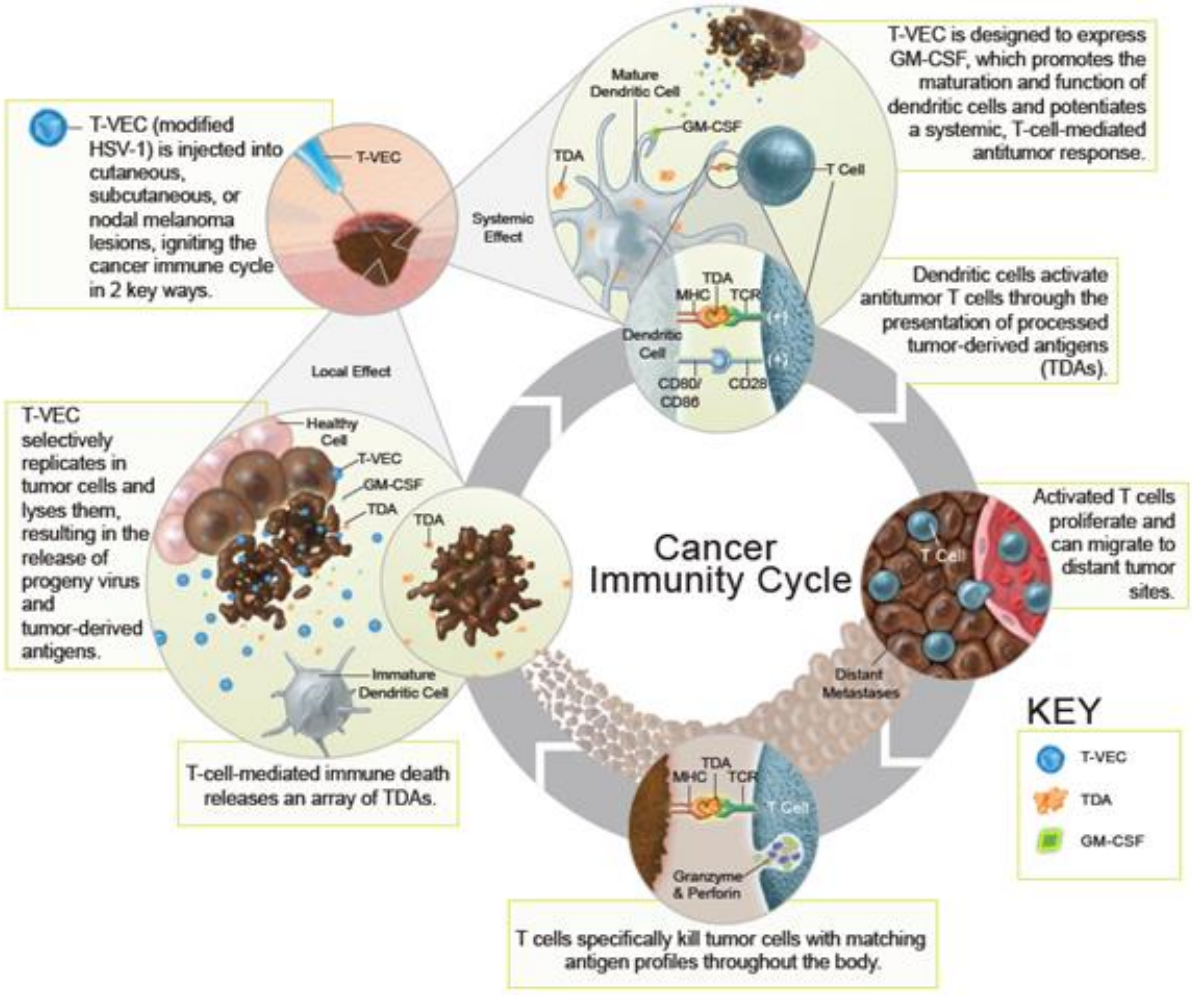
Mechanism of action

T-VEC is a novel, first-in-class treatment for Stage IIIB-IVM1a metastatic melanoma that is derived from herpes simplex virus type-1 (HSV-1) with particular modifications: deletion of the ICP34.5 neurovirulence factor gene, restricting viral pathogenicity and replication and replication within normal tissues while still allowing replication within tumours; deletion of the ICP47 gene, which enhances antigen presentation and promotes viral replication in HSV infected tumour cells and insertion of the human GM-CSF gene to stimulate anti-tumour immune responses[3,4].

T-VEC is injected intralesionally into cutaneous, subcutaneous, and/or nodal lesions that are visible on the skin, palpable, or detectable with ultrasound guidance and has two complementary mechanisms of action in/on cancerous cells[4]: i) replication that causes cell rupture/lysis and death (intracellular or direct effect) ii) post-lysis release of tumour-derived antigens and GM-CSF, stimulating a systemic immune response from antigen-presenting cells (APCs) upon distant tumour sites (extracellular or indirect effect).

The dual intracellular and extracellular mechanism of action of T-VEC can be seen in Figure 2-1.

Figure 2-1: Dual mechanism of action of T-VEC

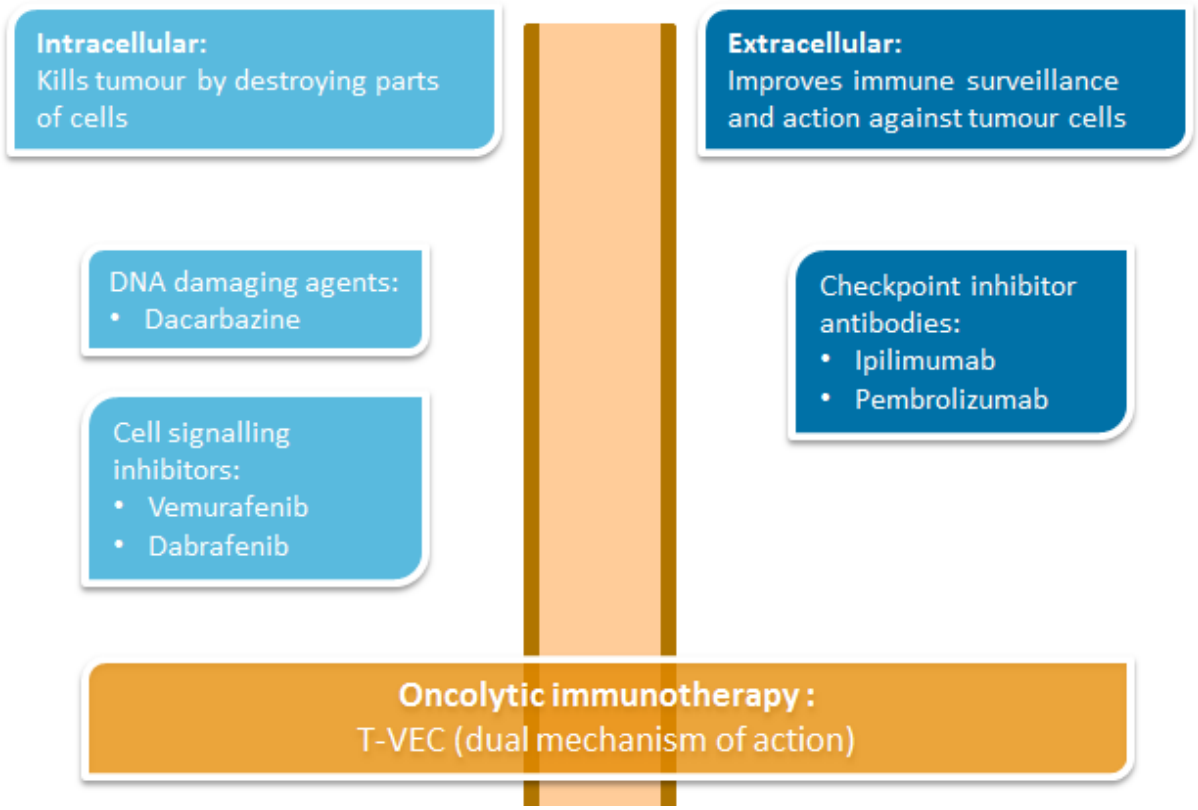


GM-CSF, granulocyte-macrophage colony stimulating factor; HSV-1, herpes simplex virus type-1; MHC, major histocompatibility complex; TCR, toll-cell receptor; TDA, tumour-derived antigens; T-VEC, talimogene laherparepvec

Source: Andtbacka et al 2014[5]

T-VEC is the only therapy for advanced melanoma which is administered intralesionally[4]. Whilst other treatments for advanced melanoma possess either an intracellular or extracellular mechanism of action (Figure 2-2), T-VEC is the only therapy that possesses a dual intracellular and extracellular mechanism of action, and represents an innovative approach to the treatment of metastatic melanoma[3].

Figure 2-2: Intracellular and extracellular mechanisms of action of therapies used in the treatment of advanced or metastatic melanoma



Reference: Luke et al 2013[6]; Medac 2014[7]; Merck 2015 [8]

T-VEC, talimogene laherparepvec

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation

Talimogene laherparepvec does not currently have a UK marketing authorisation. A marketing authorisation application (MAA) was made to the European Medicines Agency (EMA) on 2 September 2014 via the centralised process.

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending that Imlygic™ (talimogene laherparepvec) be granted approval '*for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease'* on 23 October 2015[9]. If approved by the European Commission, marketing authorisation for T-VEC in all European Union Member States is expected in December 2015. The anticipated date of availability in the UK is January 2016.

Main issues discussed by the regulatory organisation

During the CHMP review of the T-VEC application for marketing authorisation, issues were raised regarding GM-CSF as a comparator, patient population (disease stage and line of

therapy) and overall survival benefit. Please refer to the EPAR in Appendix 1.1 for full details.

Regulatory approval outside the UK

Regulatory approval for T-VEC from the Food and Drug Administration (FDA; US) was obtained in October 2015.

Other health technology assessments (HTAs) in the UK

T-VEC will be subject to appraisal by the Scottish Medicines Consortium (SMC) and the National Centre for Pharmacoeconomics (NCPE) in accordance with their remit to assess newly licensed medicines. We anticipate making submissions for T-VEC in Q1 2016, and anticipate publication of advice in accordance with their timelines and submission scheduling process.

2.3 Administration and costs of the technology

A brief overview of the administration and costs of T-VEC is provided in Table 2-1.

Table 2-1: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	10^6 (1 million) PFU/mL vial = Clear to semi-translucent liquid following thaw from its frozen state 10^8 (100 million) PFU/mL vial = Semi-translucent to opaque liquid following thaw from its frozen state The liquid in single-use vials may contain white, visible, variously shaped, virus-containing particles	Draft SmPC[4] (see Appendix 1.1)
Acquisition cost (excluding VAT) *	Anticipated list price (not final and subject to change): 1mL 10^6 PFU/mLVial or 1mL 10^8 PFU/mLVial = £1,445.00 A PAS for T-VEC has been proposed and is currently under consideration by PASLU	Draft SmPC[4] (see Appendix 1.1)
Method of administration	Intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance	Draft SmPC[4] (see Appendix 1.1)
Doses	The total injection volume for each treatment visit should be a maximum of 4 mL	Draft SmPC[4] (see Appendix 1.1)
Dosing frequency	The initial recommended dose is up to a maximum of 4 mL of T-VEC at a concentration of 10^6 (1 million) PFU/mL. The second dose is 3 weeks after the initial dose, and subsequent doses are biweekly up to 4 mL of T-VEC at a concentration of 10^8 (100 million) PFU/mL	Draft SmPC[4] (see Appendix 1.1)
Average length of a course of treatment	Treatment with T-VEC should be continued for at least 6 months unless the physician considers that the patient is not benefitting from treatment or that other treatment is required	Draft SmPC[4] (see Appendix 1.1)
Average cost of a course of treatment	The average cost of a course of treatment is [redacted]. This is based on [redacted] for the first dose and [redacted] for subsequent doses including wastage and assuming [redacted]	OPTiM CSR

	Cost	Source
	treatment duration	
Anticipated average interval between courses of treatments	3 weeks from the initial treatment visit to second treatment visit and 2 weeks for subsequent treatment visits (including re-initiation)	Draft SmPC[4] (see Appendix 1.1)
Anticipated number of repeat courses of treatments	Treatment T-VEC may be reinitiated if new lesions appear following a complete response and the physician considers that the patient will benefit from treatment.	Draft SmPC[4] (see Appendix 1.1)
Dose adjustments	No dose adjustment is anticipated	Draft SmPC[4] (see Appendix 1.1)
Anticipated care setting	T-VEC is anticipated to be administered in hospital setting as a day case only	
PAS, patient access scheme; PFU, plaque forming units; T-VEC, talimogene laherparepvec		

2.4 Changes in service provision and management

It is anticipated that T-VEC will be administered in the hospital outpatient setting in a designated side room.

Since T-VEC is a live virus it is expected that it would be administered in key centres of excellence with established oncology units that already provide the staffing and infrastructure for the administration of cancer treatments. Additionally, these centres will have appropriate facilities for the storage, administration and disposal of viral products and it is anticipated that there may be some increased use of the services of nurses or clinicians to deliver T-VEC.

It is not anticipated that T-VEC will be associated with additional monitoring requirements as patients would be monitored on an ongoing basis at routine appointments.

2.5 Innovation

T-VEC is a first-in-class oncolytic immunotherapy with a dual mechanism of action that produces local tumor control as well as systemic anti-tumor immune responses. Whilst other treatments for metastatic melanoma possess either an intracellular or extracellular mechanism of action, T-VEC is the only therapy that possesses a dual mechanism of action and is also the only treatment that is administered intralesionally (see Section 2.1).

T-VEC is the only treatment approved specifically in patients with regionally or distantly metastatic melanoma with no visceral disease (IIIB-IVM1a) and has demonstrated a major clinical advancement in treatment for this population. It is the only treatment with a demonstrated OS benefit in this population; 1 in 6 patients treated with T-VEC achieved CR, with the majority of responses achieved being durable (≥6 months). T-VEC reduces the risk of developing visceral metastasis by 59% and increases the median OS by over 2 years. More than half of patients treated with T-VEC were alive at 3 years, and the survival rate

appears to be stable over 4 and 5 years. In addition, T-VEC has one of the lowest percentages of treatment-related grade 3/4 AEs among existing treatment options.

T-VEC therefore represents a valuable new treatment option for patients with regionally or distantly metastatic melanoma with no visceral disease, aiming to delay/prevent relapses or progression to later stages of metastatic disease, and positively improve OS.

3 Health condition and position of the technology in the treatment pathway

- Melanoma is a rare but serious skin cancer that can rapidly infiltrate deep, vascular skin layers, and can commonly metastasise very early
- Malignant melanoma is the fifth most common cancer in the UK, where over 13,000 new cases are diagnosed a year
- Over 2,000 deaths per year in the UK can be attributed to melanoma – chances of survival diminish markedly for later stage metastatic disease. The treatment paradigm in melanoma continues to expand, with recently licensed treatments, recommended by NICE, rapidly becoming the new standard of care. However the majority of patients still die from their disease, therefore there remains an unmet need for clinically effective treatments
- BRAF inhibitors, which report high response rates but with limited duration are only indicated for patients with BRAF-mutant melanoma (who constitute 40% to 50% of the patient population). Whilst immunomodulators, such as ipilimumab, which show a lower, but more durable response rates, can result in significant toxicity
- The evidence base for existing agents in patients with non-visceral metatstic disease is minimal, and currently none has demonstrated an ability to delay or prevent disease progression to visceral disease in regionally metastatic melanoma
- For patients with non-visceral metastatic disease, there remains an unmet need for effective therapies that provide a high and durable response rate, a long term survival benefit, combined with an improved safety profile
- Therefore, novel therapeutic approaches for metastatic melanoma that increase the number of patients achieving CR, delay or prevent progression to visceral metastases, and increase the number of patients surviving long term with lower risk of severe toxicities would help address existing unmet medical needs

3.1 Overview of malignant melanoma

Pathophysiology

Melanoma is a malignancy of pigment-producing cells in the skin called melanocytes[10]. Superficial spreading melanoma, nodular melanoma, and lentigo maligna melanomas make up 90% of all diagnosed malignant melanomas. Acral lentiginous melanoma and a few very rare types together make up the other 10%[11].

Malignant melanoma is associated with high mortality due to the potential for: fast progression of disease; sudden relapse of disease[12]; and a greater likelihood than other skin cancers to metastasise to distant hard to treat sites in the body[13] The most common sites to which melanoma metastasises are lymph nodes, lung, liver, and brain[14], but it can metastasise to almost any organ and may affect many sites simultaneously[15-17].

If melanoma is detected before cancer cells have reached the blood vessels that are deeper in the skin, it can usually be completely removed with surgery. However, melanoma is often not detected in its earliest stages because the patient may not notice or bring attention to the

lesion, or the clinician may not detect the melanoma at an examination[18]. Not all tumours show the commonly accepted warning signals (often denoted by the acronym "ABCD": Asymmetry, irregular Borders, multiple Colours, and Dynamics [change over time]), and some melanomas appear similar in appearance to benign melanocytic nevi (moles)[19]. In addition, some patients lack important risk factors for melanoma, such as the presence of a large number of nevi and freckles[20].

The development of melanoma depends on intrinsic factors, such as skin type or gene mutations, and extrinsic factors, the most relevant of which is exposure to ultraviolet (UV) radiation[21].

Disease staging

Melanoma is considered advanced, and described as metastatic melanoma, if it has spread to surrounding lymph nodes (stage III) or to other parts of the body (stage IV). Malignant melanoma is classified in metastatic sub-stages, which encompass[22]:

Unresectable stage III disease (stage III) with regional skin and/or lymph node involvement **or**

Distant metastatic disease (stage IV), to any site, with location either in:

- skin (distant cutaneous or subcutaneous tissue) or distant lymph nodes (M1a)
- lung (M1b)
- any visceral organ and/or increased lactate dehydrogenase (LDH) levels in the serum, indicating aggressive tumour growth (M1c).

Incidence and survival

Malignant melanoma is the fifth most common cancer in the UK with a total of 13,348 new cases diagnosed in 2011 (latest year available), accounting for 4% of all cancers in both males and females in the UK[23]. The incidence of melanoma in the UK has risen sharply in recent years, largely owing to lifestyle choices[24]. Although the increase in incidence may in part be attributable to improved surveillance and changes in diagnostic criteria, the main reason is believed to be linked to changes in sun-related behaviour and exposure to UV radiation (e.g. increased frequency of holidays)[23].

In the UK, malignant melanoma was responsible for 2,148 deaths in 2012 (latest year available)[25]. Survival of patients with melanoma has improved over recent decades potentially due to increased awareness and earlier diagnosis of the disease as a result of public health campaigns[26]. Survival rates for malignant melanoma vary dramatically according to the stage of the disease at diagnosis: Poorest survival is seen in patients diagnosed with stage IV disease, with 1-year survival rates falling to 10% for men and 35% for women. However these estimates have wide confidence intervals due to small patient numbers[26].

3.2 Effects of the disease or condition on patients, carers, and society

Melanoma is a deadly form of skin cancer, causing 90% of skin cancer-related deaths[27-29]. Although melanoma affects people of all ages, 34% of patients are younger than 55 years at

diagnosis, thereby resulting in substantial impact on work and life productivity, particularly if their disease becomes metastatic. Overall survival (OS) differs by stage of metastatic disease; however, even patients with non-visceral metastatic melanoma have a shorter median OS compared to patients with many other cancers.

When the age distribution and the lethality of metastatic disease are taken together, the result is more years of life lost per patient due to melanoma compared with many other cancers. Malignant melanoma was found to result in an average of 23.2 years lost per patient, making it one of the leading causes of lost life years due to cancer. Recent research estimating years of life lost due to melanoma found that people who die from melanoma, die an average of 20 years prematurely; that is, their life expectancy compared with the general population is shortened by 20 year[30,31]. Thus, mortality rates alone do not tell the whole story of the impact of melanoma on public health. Since the years of healthy life lost with melanoma is higher compared with most other cancers, the societal burden from melanoma is significant[32].

Melanoma can result in substantial impairment in health-related quality of life and psychological functioning. People with melanoma face many physical, emotional, and psychological challenges. A systematic review of quality-of-life studies in melanoma found that, although patients with metastatic disease have a high level of functioning when they are first diagnosed, the rapid progression of their disease leads to a decline in almost all of the major physical and social functional domains[33]. Melanoma lesions can be of irregular shape and colour and cause facial or bodily disfigurement[34-36]. In addition, obtaining adequate surgical margins for excision often results in substantial cosmetic disfigurement or functional morbidity[37]. Changes in physical appearance resulting from melanoma can cause psychological distress and a reduction in feelings of self-esteem, self-confidence, and social comfort interacting with others[38-40].

In addition to the devastating and long-lasting impact of the condition itself, people with melanoma can incur substantial time lost from work while on treatment. Lost productivity and travel costs incurred while receiving treatments further contribute to the societal burden of melanoma and can impact caregivers as well. Recent studies have reported that among cancers, melanoma is the second leading cause of lost productive work years. As many as 45% of melanoma deaths occur before retirement age[41].

Melanoma poses a substantial economic burden to society. Malignant melanoma has been found to be associated with a total societal cost of £138 million in England in 2002. Substantial morbidity and mortality resulting in lost life years contributes to the economic burden of melanoma. The estimated costs of melanoma-related productivity losses are substantial[42]. A recent study estimating the cost of lost productivity due to cancer-related premature mortality for all cancers in Europe showed that melanoma had the highest average lost-productivity cost per death (€312,798)[43]. The collective evidence on mortality, health-related quality of life, lost life years, and lost productivity, experienced even with the availability of existing treatment options for this deadly condition, emphasises the need for further research and funding for the management of malignant melanoma in England.

3.3 Description of clinical pathway of care

Aims of therapies

Goals of treatment for unresectable metastatic melanoma (stage IIIB-IV) vary dependent on metastatic sub-stages (as defined in Section 3.1).

- ***Non-visceral disease (stage IIIB-IVM1a)*** i.e. patients with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease *(Stage IIIB, IIIC and IVM1a)*. For these patients, the goal of treatment is to maintain local and regional control and delay/prevent relapse or progression to visceral disease[44], since the delay/prevention of visceral disease is important to the goal of long-term survival.
- ***Visceral disease (stage IVM1b and IVM1c)*** i.e. patients with unresectable, melanoma; with distant metastatic disease in lung or any visceral organ and/or increased lactate dehydrogenase (LDH) in the serum, indicating aggressive tumour growth (Stage IVM1b and IVM1c). For these patients a cure is rare. Therefore the aim of systemic drug treatment is to prolong survival and decrease symptoms by reducing tumour size or load[10]

In all stages of metastatic melanoma, the key aim is to improve long term survival. OS is correlated with both level and durability of response/complete response to treatment. Importantly, complete response (i.e. the disappearance of all signs of cancer) significantly correlates with long-term survival in melanoma[45,46].

Description of current treatment options

Treatments for metastatic melanoma include biological therapy, chemotherapy, radiotherapy or surgery. In the UK, patients with regional or distant metastases have traditionally been treated with dacarbazine (DTIC), although no clinically meaningful improvement in OS has been demonstrated in randomised controlled trials. However since 2011, a range of new agents have been approved by the EMA (Table 3-1).

These recently licensed treatments have a range of differing modes of action; including CTLA-4 anti-bodies, BRAF inhibitors, MEK inhibitors and Anti-PD-1s. All are licensed in previously treated and untreated patients. Many of these agents are limited in their licensed population by biomarker expression, although none distinguish between stages and subs-stages of metastatic melanoma. None of them have been studied extensively in patients with unresectable stage IIIB, IIIC or IVM1a melanoma; who made up only 11% and 17% of patients in ipilimumab RCTs, 18% of patients in vemurafenib RCTs and 10% of patients in dabrafenib RCTs.

Table 3-1: Recently approved drugs for the treatment of advanced or metastatic melanoma

Therapy	Class	Year of EMA Approval	Current Indication
Ipilimumab (Yervoy®; BMS)[47] Monotherapy	CTLA-4 antibody	2011	Previously untreated and treated patients For the treatment of advanced (unresectable or metastatic) melanoma in adults

Therapy	Class	Year of EMA Approval	Current Indication
Vemurafenib (Zelboraf®; Roche)[48] Monotherapy	BRAF inhibitor	2012	Previously untreated and treated patients with *BRAF* V600 mutation For the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma
Dabrafenib (Tafinlar®; Novartis)[49,50] Monotherapy or in combination with trametinib	BRAF inhibitor	2013	Previously untreated and treated patients with *BRAF* V600 mutation For the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Trametinib (Mekinist®; Novartis)[50,51] Monotherapy or in combination with dabrafenib	MEK inhibitor	2014	Previously untreated and treated patients with *BRAF* V600 mutation For the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy
Nivolumab (Opdivo®, BMS)[52] Monotherapy	Anti-PD-1	2015	Previously untreated and treated patients For the treatment of advanced (unresectable or metastatic) melanoma in adults
Pembrolizumab (Keytruda®, Merck)[53] Monotherapy	Anti-PD-1	2015	Previously untreated and treated patients For the treatment of advanced (unresectable or metastatic) melanoma in adults
Combination of vemurafenib and cobimetinib (Roche)[54]	Combination of BRAF and MEK inhibitors	2015	Previously untreated and treated patients with *BRAF* V600 mutation For the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Abbreviations: BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte antigen-4; EMA, European Medicines Agency			

Summary of NICE clinical guidelines, guidance and local guidelines

Two Clinical Guidelines (CGs) and six Technology Appraisals (TAs), providing guidance on the management and treatment of advanced or metastatic melanoma, have been published by NICE, with the recommendations outlined in Table 3-2. This includes the final appraisal determination from the most recent TA [ID801], appraising pembrolizumab in ipilimumab treatment naïve patients, with full publication due in November 2015.

Table 3-2: Summary of published NICE technology appraisals for advanced or metastatic melanoma

Clinical guideline/Technology Appraisal	Guideline recommendations
CSGSTIM 2010. Improving Outcomes for People with Skin Tumours including Melanoma (replaced previous guidelines published in 2006)	[No specific treatment recommendations - outlines how healthcare services for people with skin tumours should be organised]
NG14 2015. Melanoma: assessment and management of melanoma	Dacarbazine may be considered for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable (Note, the time of publication [July 2015], dacarbazine did not have a UK marketing authorisation for this indication) Do not offer further cytotoxic chemotherapy for stage IV metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial [Reader referred to individual TAs for other treatments for metastatic melanoma]
TA268 2012. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma	Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the PAS
TA269 2012. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma	Vemurafenib is recommended as an option for treating BRAF V600 mutation positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the PAS
TA319 2014. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma	Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the PAS For patients who have BRAF V600 mutation positive melanoma, the Committee heard that vemurafenib was likely to remain the standard first-line treatment option especially in those with high disease burden, but understood that ipilimumab would be valuable as a first-line option in approximately 20%-30% of patients with small-volume indolent disease for whom vemurafenib could be reserved as rescue treatment later in the pathway
TA321 2014. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‑positive melanoma	Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation positive melanoma only if the company provides dabrafenib with the discount agreed in the PAS

Clinical guideline/Technology Appraisal	Guideline recommendations
TA357 2015. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab	Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only: after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor and when the company provides pembrolizumab with the discount agreed in the PAS
[ID801] Pembrolizumab for advanced melanoma not previously treated with ipilimumab	Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the company provides pembrolizumab with the discount agreed in the patient access scheme
References: CSGSTIM[55]; NG14[56]; TA268[57]; TA269[58]; TA319[2]; TA321[1]; TA357[59]; ID801[60] PAS, patient access scheme * MEK inhibitors have not been formally recommended by NICE for use in England and Wales for advanced or metastatic melanoma	

NICE TAs in development for metastatic melanoma

A total of seven TAs are currently in development for other treatments for advanced or metastatic melanoma, and are listed below.

- Melanoma (advanced and metastatic) – temozolomide [ID316]. Expected date of issue to be confirmed.
- Melanoma (metastatic) – paclitaxel albumin-bound nanoparticles (first-line) [ID570]. Expected date of issue to be confirmed.
- Melanoma (advanced, unresectable, metastatic) – nivolumab [ID845]. Expected May 2016.
- Melanoma (BRAF V600, advanced, unresectable, metastatic) – cobimetinib (with vemurafenib) [ID815]. Expected June 2016.
- Melanoma (BRAF V600E mutation positive, unresectable, metastatic) – dabrafenib and trametinib [ID661]. Expected August 2016.
- Melanoma (untreated, advanced, unresectable, metastatic) – nivolumab (with ipilimumab) [ID848]. Expected September 2016.

Other clinical treatment guidelines

Treatment guidelines have also been published by the British Association of Dermatologists (BAD) and a multidisciplinary consortium of European clinical societies, namely the EDF, EADO and EORTC, however these clinical guidelines were published in 2010 and therefore precede the introduction of the targeted therapies[61,62].

The BAD recommended dacarbazine for the treatment of metastatic melanoma, with the acknowledgement that its role is palliative[61]. It also noted that though high-dose interleukin-2 has not been evaluated in a randomised Phase III trial a small minority of patients may experience durable complete responses and patients with stage IV melanoma should be considered for entry to clinical trials[61].

In response to advances in the therapy of metastatic melanoma, the EDF, EADO and EORTC, recommended mutation testing of tumour tissue (at least BRAF; CKIT in subtypes) prior to treatment decisions[62]. BRAF inhibitors or experimental drugs blocking the MAP kinase and PI3K pathways were recommended for BRAF mutated patients and ipilimumab offered to both BRAF and non-BRAF-mutated patients[62]. A treatment algorithm was not established due to insufficient data[62].

In 2007, the Royal College of Physicians issued clinical guidelines outlining recommendations for identifying and referring possible patients with skin cancer for further management. However, no specific treatments are mentioned[63].

The European Society for Medical Oncology has recommended that for patients with metastatic melanoma, tumours should be tested for the presence of mutations (e.g. BRAF, NRAS, c-Kit, GNA11, GNAQ) and that treatment options for the first- and second-line setting include: ipilimumab, nivolumab and pembrolizumab for all patients; and vemurafenib, encorafenib and dabrafenib (used alone and/or in combination with MEK inhibitors like binimetinib, cobimetinib and trametinib) for patients with BRAF mutation positive disease. Note, these guidelines also state that T-VEC is a potential treatment options for unresectable in-transit cases of melanoma.[64]

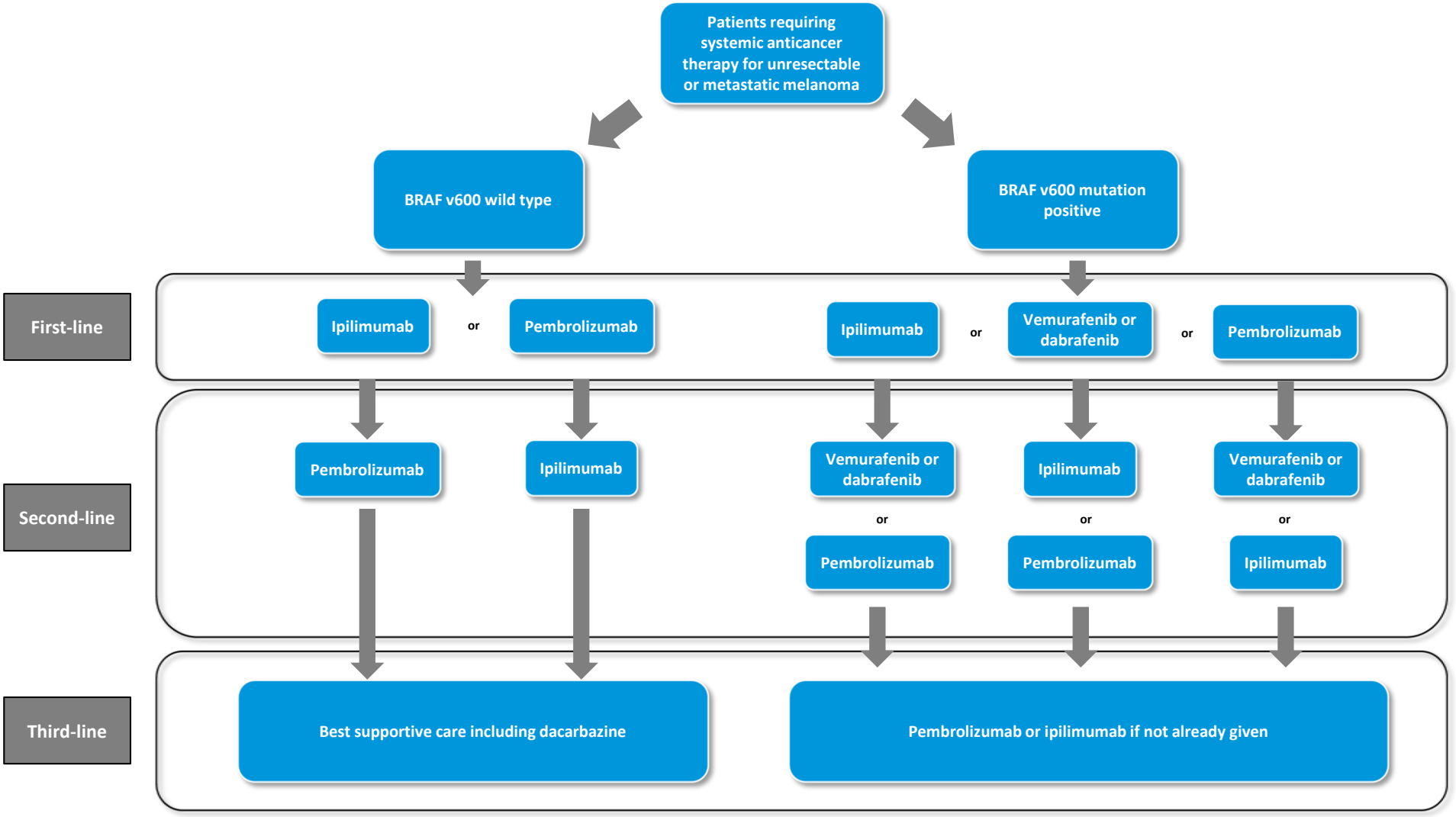
Clinical pathway of care showing the context of the proposed use of the technology

According to current NICE CGs and TAs, the current clinical pathway of care (summarised in Figure 3-1) for advanced or metastatic melanoma is based on BRAF mutation status[1,55-60]:

- Patients who are BRAFv600 mutation positive may receive first line treatment with a BRAF inhibitor (vemurafenib or dabrafenib) or with ipilimumab
- Patients who are BRAFv600 mutation negative (wild-type) may receive first line treatment with ipilimumab or pembrolizumab. Where immunotherapy/targeted therapy are not suitable, dacarbazine may be considered.

The described treatment pathway reflects NICE recommended treatments in first, second and third line by BRAF status, regardless of stage of disease. However clinical expert opinion indicates that BRAF inhibitors are more likely to be reserved for those ($BRAF^{V600}$ positive) patients with more rapidly progressing disease and high disease burden. Therefore immunomodulators, such as ipilimumab, are the likely treatment options for patients with non-visceral metastatic disease (IIIB - IVM1a), for which T-VEC is indicated.

Figure 3-1: Overview of the treatment pathway for advanced or metastatic melanoma according to recommendations from NICE



References: CSGSTIM[55]; NG14[56]; TA268[57]; TA269[58]; TA319[1]; TA321[1]; TA357[59]; ID801[60]
Note: Pembrolizumab has recently been approved by NICE but is not within the scope of this appraisal.

Limitations of current clinical treatment pathway

Metastatic melanoma is a clinically and biologically heterogeneous disease. It has been one of the most complex and resistant tumour types to treat, with high recurrence rates warranting the need for a range of treatment options. Within the UK, recently licensed treatments recommended by NICE are rapidly becoming the new standard of care, however there remains significant unmet need within the current treatment pathway;

The evidence base for ipilimumab and BRAF inhibitors in patients with non-visceral metastatic disease is minimal.

The majority of data relating to existing agents are from patients with later stage metastatic disease (stages M1b and M1c); none has been studied extensively in patients with unresectable stage IIIB, IIIC or IVM1a melanoma, making up only 11% and 17% of patients in ipilimumab RCTs, 18% of patients in vemurafenib RCTs and 10% of patients in dabrafenib RCTs. It is expected that efficacy would be better in patients with non-visceral metastatic disease; however the magnitude of OS gain for these agents is uncertain.

None of the existing therapies have demonstrated an ability to delay or prevent disease progression to visceral disease in regionally metastatic melanoma.

The risk of developing visceral metastases is high in patients with stage IIIB/C and IVM1a melanoma. Over 60% of patients with stage IIIB/C and IVM1a disease will eventually progress to visceral disease (stage IVM1b/c)[22,65,66]. Although visceral disease is associated with additional symptom burden to patients[67] and increased treatment costs to payers[68,69], none of the existing therapies have demonstrated an ability to delay or prevent metastatic disease progression to visceral disease in patients with metastatic melanoma because significant numbers of patients without visceral disease were not included in the clinical studies.

Existing therapies report low rates of complete response (strongly associated with long-term survival) and low 5-year survival rates.

Melanoma survival is associated with stage of metastatic disease and the ability to induce DR or CR. CR refers to the disappearance of all signs of cancer in response to treatment, and significantly correlates with long-term survival in melanoma[45,46]. Given that a substantial proportion of patients with melanoma are younger, it is important for these patients to achieve CR and long-term survival. However, RCT evidence from the pivotal studies for ipilimumab and the BRAF inhibitors report that CR rates remain relatively low; CR was achieved in only 2 patients (1.5%) treated with ipilimumab[70], two patients (<1%) receiving vemurafenib (BRIM-3) and 6 patients (3%) receiving dabrafenib[64,71]. Importantly, evidence from existing treatments show that the number of patients surviving beyond 5 years remains low.

Overall Response Rates and Duration of Responses are variable with existing treatments

In the pivotal ipilimumab phase 3 trial the ORR was relatively low, 10.9% however 60% of responses lasted at least 2 years[70]. Conversely the ORR with *BRAF* was 48%-53%, however the median duration of response ranged from 5.5 to 6.7 months[71]. The short duration of response with *BRAF* inhibitors may be related to treatment resistance.

Existing therapies can result in significant toxicity, which complicates treatment and affects quality of life for many metastatic patients, and are of particular concern for those with non-visceral metastatic disease.

Existing therapies can result in significant toxicity, which complicates treatment and affects quality of life for many patients already struggling with metastatic melanoma. Treatment with ipilimumab is associated with a number of grade 3 or 4 AEs, which may involve the gastrointestinal, liver, skin, nervous, endocrine, ocular, or other organ systems[47,72,73]. In some cases, the toxicities occurred in patients many weeks or even months after receiving the last dose of [74]. In the pivotal phase 3 ipilimumab trial of previously treated patients, 23% of patients receiving ipilimumab monotherapy developed drug-related grade 3 or 4 toxicities, the majority of which (15%) were immune-related. The incidence of drug-related death with ipilimumab monotherapy is 3[72]. The rate of treatment-related grade 3 or 4 AEs with vemurafenib was 43% in previously untreated patients[75] and in the vemurafenib single-arm phase 2 study in previously treated patients, grade 3 and 4 AEs were reported in 60% and 4% of patients, respectively[76].

In summary there is still a substantial unmet need within the current UK treatment pathway: The BRAF inhibitors (vemurafenib and dabrafenib) are approved only for a subset of patients with the BRAF V600 mutation, which accounts for approximately 40% to 50% of melanoma patients[77]. Whilst response rates for BRAF inhibitors are high; responses appear to be of limited duration, due to development of treatment resistance[78]. For these reasons, BRAF inhibitors are more likely to be reserved for those (BRAFV600 positive) patients with more rapidly progressing disease and high disease burden, where the rapid response provided by BRAF inhibitors is needed. Immunomodulators, such as ipilimumab, have shown a marked benefit for a small proportion of patients (whether BRAFV600 mutation positive or wild type), but show a low response rate (10.9%), with a complete response rate of less than 2%[72]. Although responses appear to be more durable than the BRAF inhibitors, this is achieved at the cost of a significant AE profile[72], with a range of treatment limiting and potentially fatal immune-related adverse events.

Clinical expert opinion suggests that for those patients with non-visceral metastatic disease and limited systemic disease, who would benefit from treatment to prevent progression to visceral disease, physicians may choose to adopt a wait and watch policy, because of the range of treatment limiting and potentially fatal immune-related adverse events associated with ipilimumab and the lack of less toxic alternatives treatment options. Therefore for patients with non-visceral disease and limited systemic disease, there remains an unmet need for effective therapies that provide a high complete response that is durable, a long term survival benefit, combined with an improved safety profile.

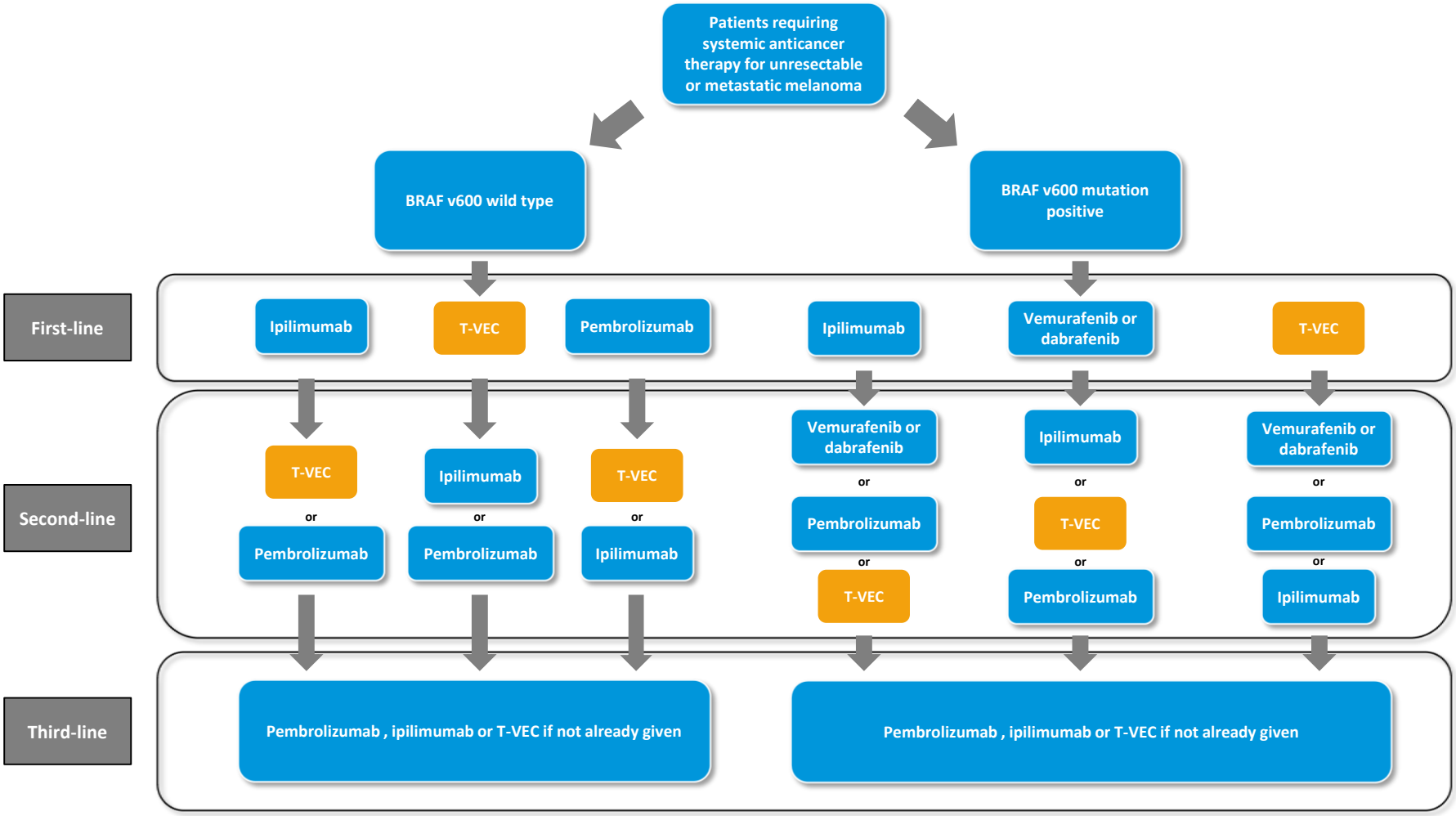
Proposed positioning within the treatment pathway and patient populations

T-VEC has demonstrated a major clinical advancement in patients with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. There is evidence of improved, or at least comparable efficacy versus the current alternative treatment, ipilimumab, combined with a very favourable safety profile. T-VEC therefore represents a valuable treatment option for these patients, to delay and/or prevent progression to later stages of disease and improve OS.

T-VEC is therefore proposed as a new treatment option for these patients, within its expected indication, as an alternative treatment to the currently recommended treatment: ipilimumab.

Clinicians in the UK support the proposed positioning of T-VEC within the current treatment pathway as shown in Figure 3-2.

Figure 3-2: Proposed position of T-VEC within the treatment pathway for patients with advanced or metastatic melanoma in accordance with existing recommendations from NICE



Note, pembrolizumab has been recently approved by NICE but is not within the scope of this appraisal

Selection of Comparators

T-VEC is proposed as a treatment option for patients with unresectable melanoma that is regionally or distantly metastatic, with no bone, brain, lung or visceral disease (IIIB-IVM1a), i.e. early stage disease. Ipilimumab, dabrafenib and vemurafenib are all licensed for the broad population of advanced (unresectable or metastatic) melanoma in adults (which includes the subgroup of patients with stage IIIB-IVM1a) and are defined as relevant comparators in the decision problem. Vemurafenib and dabrafenib are only approved for a subset of patients with the BRAF V600 mutation, which accounts for approximately 40% to 50% of melanoma patients.

In clinical practice patients with non-visceral metastatic disease are routinely treated with immunotherapies rather than BRAF inhibitors, except where there is evidence of rapidly progressing disease and high disease burden (NICE guidance (TA319)[2] and expert opinion) i.e. later stage metastatic disease (stage IVM1b-IVM1c). Therefore of the comparators defined in the decision problem, only ipilimumab, like T-VEC, is indicated for all patients regardless of BRAF status and is also the likely treatment option for the stage IIIB-IVM1a disease for which T-VEC is indicated.

For these reasons the primary comparator for licensed T-VEC population is considered to be ipilimumab, although all three comparators are evaluated within the submission.

Issues relating to clinical practice including any variations or uncertainty about best practice

The management of advanced melanoma is rapidly evolving with several ongoing clinical trials and there is uncertainty about how these treatments will be sequenced in the future. Despite the emergence of further systemic therapies (e.g. with BRAF inhibition in combination with MEK inhibition, and anti CTLA4 therapy potentially in combination with anti-PD1 therapy), there is still value for treatments with improved tolerability, that target patients with limited metastatic disease and readily injectable disease, regardless of what further lines of optimal systemic therapy evolve.

3.4 Life expectancy of patients with the disease

Survival for malignant melanoma is related to the stage of the disease at diagnosis[26]. When diagnosed at an early stage, melanoma is a potentially curable by surgical resection of the tumour, however advanced disease is associated with an extremely poor prognosis. Although the treatment of malignant melanoma has progressed in recent years there is still a low 5-year survival rate of 20% to 34% for patients with stage IIIC disease and 5% to 22% for stage IV disease[26].

The number of expected incident cases of malignant melanoma for 2015 in England is estimated to be 15,317 (see Section 6). The projected number of patients eligible for treatment with T-VEC in the next 5 years is presented in Table 3-3. The estimate was based on a population of adult patients with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease Table 3-3.

Table 3-3: Estimated eligible adult population with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease

Assumption	Year 1	Year 2	Year 3	Year 4	Year 5
	2015	2016	2017	2018	2019
Estimate of incident melanoma population in 2015 (all stages)	15,317	15,853	16,408	16,982	17,577
Proportions of patients with stage IIIB – IVM1a disease	1,424	1,474	1,526	1,579	1,635
Proportions of patients with injectable disease	1,040	1,076	1,114	1,153	1,193
Proportions of patients diagnosed with metastatic or unresectable melanoma in whom chemotherapy/active treatment is suitable	728	753	780	807	835
Eligible patients	728	753	780	807	835

3.5 Equality Issues

We are unaware of any equality issues that could impact on this appraisal.

4 Clinical effectiveness

- T-VEC has demonstrated a major clinical advancement in the treatment of patients with regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease (IIIB-IVM1a).
- Evidence comes from the pivotal phase III OPTiM study, evaluating a subgroup of 249 patients with stage IIIB-IVM1a malignant melanoma
- Evaluation of response rates showed a CR rate of 16.6% in the T-VEC arm compared to 0.0% in the GM-CSF arm (P<0.001) (1 in 6 patients treated with T-VEC achieved CR in this population) and an ORR (CR + PR) of 40.5% in the T-VEC arm versus 2.3% in the GM CSF arm (P<0.0001)
- The ORR results achieved with T-VEC were generally durable; a DRR of 25.2% was observed in the T-VEC arm versus 1.2% in the GM-CSF arm (odds ratio [OR] was 28.6 [95% CI: 3.9, 211.5]; P<0.0001)
- T-VEC also produced a median OS gain of 25.3 months versus GM-CSF (46.8 vs 21.5 months, p=0.0008 in the final data cut)
- The challenges of a disconnected network and the significant differences in RCT patient populations meant that a NMA was not feasible.
- Evaluation of alternative methods for comparing survival outcomes for T-VEC versus ipilimumab identified the Korn predicted equation as the most suitable
- The modified Korn method, which was used to predict OS for ipilimumab, assuming the baseline characteristics of the T-VEC licensed trial population (using the prognostic variables of gender, ECOG performance status, visceral status, brain metastases and high LDH) predicted a median OS of 21.3 months.
- The two-step Korn method, which assumed an interaction effect between the ipilimumab treatment and the non-visceral disease patient population, predicted a median OS of over 40 months (median OS not reached) for ipilimumab. This compared to the observed a median OS of 46.8 months for T-VEC in the same patient population of the OPTiM RCT
- Comparing survival outcomes for T-VEC versus ipilimumab using the modified Korn method resulted in a favourable OS for T-VEC. Using the two-step Korn method reduced the difference but was still favourable for T-VEC. An open-label phase II clinical trial (Study 002/03) also demonstrated efficacy outcomes that were in line with the OPTiM study
- Adverse events (AEs) associated with T-VEC (e.g. pyrexia, chills, flu-like symptoms, and injection site reactions) are mostly mild and generally manageable by means of supportive care.
- Rates of study drug discontinuation due to treatment-related AEs were low with T-VEC treatment, with a total of 2.4% and 2.5% of treated patients in the ITT population and in the subgroup of patients with no visceral disease, respectively, discontinuing study treatment because any grade treatment-related adverse events

4.1 Identification and selection of relevant studies

To assess the comparative efficacy of T-VEC compared with ipilimumab, vemurafenib and dabrafenib, a broad systematic review of RCT and non-RCT evidence for treatments in advanced malignant melanoma was conducted. Additional exclusion criteria were applied to this broad review to further align the results with the decision problem and to identify studies most relevant for inclusion in this submission, as detailed below. Appendix 1.2 presents further details of search strategy, eligibility criteria, data extraction, quality assessment, lists of included studies,and excluded studies (and reasons for exclusion) and overview of studies included in the qualitative synthesis.

Search strategy

Search strategies were developed specifically for each database and keywords adapted according to the configuration of each database. Searches were not limited by date, language, or publication status (published, unpublished, in press, and in progress).

The following databases were searched for relevant studies:

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.

Supplementary searches were undertaken for the following trials registers from inception to March 2015:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP)
- EU Clinical Trials Register (EUCTR) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- PharmaNet.bu registries
- National Institutes of Health (NIH) Clinical Trial Registry (CTR)
- Australian New Zealand Clinical Trials Registry (ANZCTR) (http://www.anzctr.org.au/TrialSearch.aspx)

Further supplementary searches were undertaken in relevant conference abstracts from 2013 to present:

American Society of Clinical Oncology (ASCO)

- 2013 http://meetinglibrary.asco.org/abstractbysubcategory/2013%20ASCO%20Annual%20Meeting/561
- 2014 http://meetinglibrary.asco.org/abstractbysubcategory/2014%20ASCO%20Annual%20Meeting/561
- 2015 http://meetinglibrary.asco.org/meeting/2015%20ASCO%20Annual%20Meeting

European Society for Medical Oncology (ESMO)

- 2013 No conference held in 2013
- 2014 http://annonc.oxfordjournals.org/content/25/suppl_4.toc

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

- 2013 http://www.ispor.org/publications/value/JVAL_16-3_FINAL.pdf
- 2014 http://www.ispor.org/publications/value/VIH_17-3_final.pdf

- 2015 http://www.ispor.org/publications/value/VIH_18-3_final.pdf

European Association of Dermato Oncology (EADO)

- 2013 http://onlinelibrary.wiley.com/doi/10.1111/ddg.12162/epdf
- 2014 http://www.eado2014.com/
- 2015 expected October 28-31, 2015

European Cancer Congress (ECC)

- 2013 http://2013.europeancancercongress.org/
- 2014 Abstracts not available online
- 2015 Expected September 25-29, 2015

All search strategies are provided in Appendix 1.2.

Study selection

Study inclusion was not limited by language or publication date, and included both published and unpublished evidence. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 4-1.

Table 4-1: Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years of age) with advanced melanoma (stage III–IV) who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases • Animal, in vitro and biomarker studies
Intervention	• T-VEC, all licensed or guideline-recommended pharmacological interventions used to treat advanced or metastatic melanoma administered alone or in combination were	• Studies that do not include either the included intervention or comparator agents as one of their treatment arms • Non-drug interventions, such as surgery
Comparators	• Placebo, best supportive care, or any active interventions, including dose-to-dose comparisons	• Studies of combination therapies that did not include at least one drug of interest
Study Design	• RCTs, including crossover studies; non-randomised clinical trials; • Observational studies (prospective and retrospective cohort studies); • RCT sub studies were included if they reported data for first-line (e.g., stage IIIB, IIIB, and IVMIa) melanoma patients, additional outcomes of interest (e.g., separate HRQoL report), or long-term follow-up data (e.g., open label extensions).	

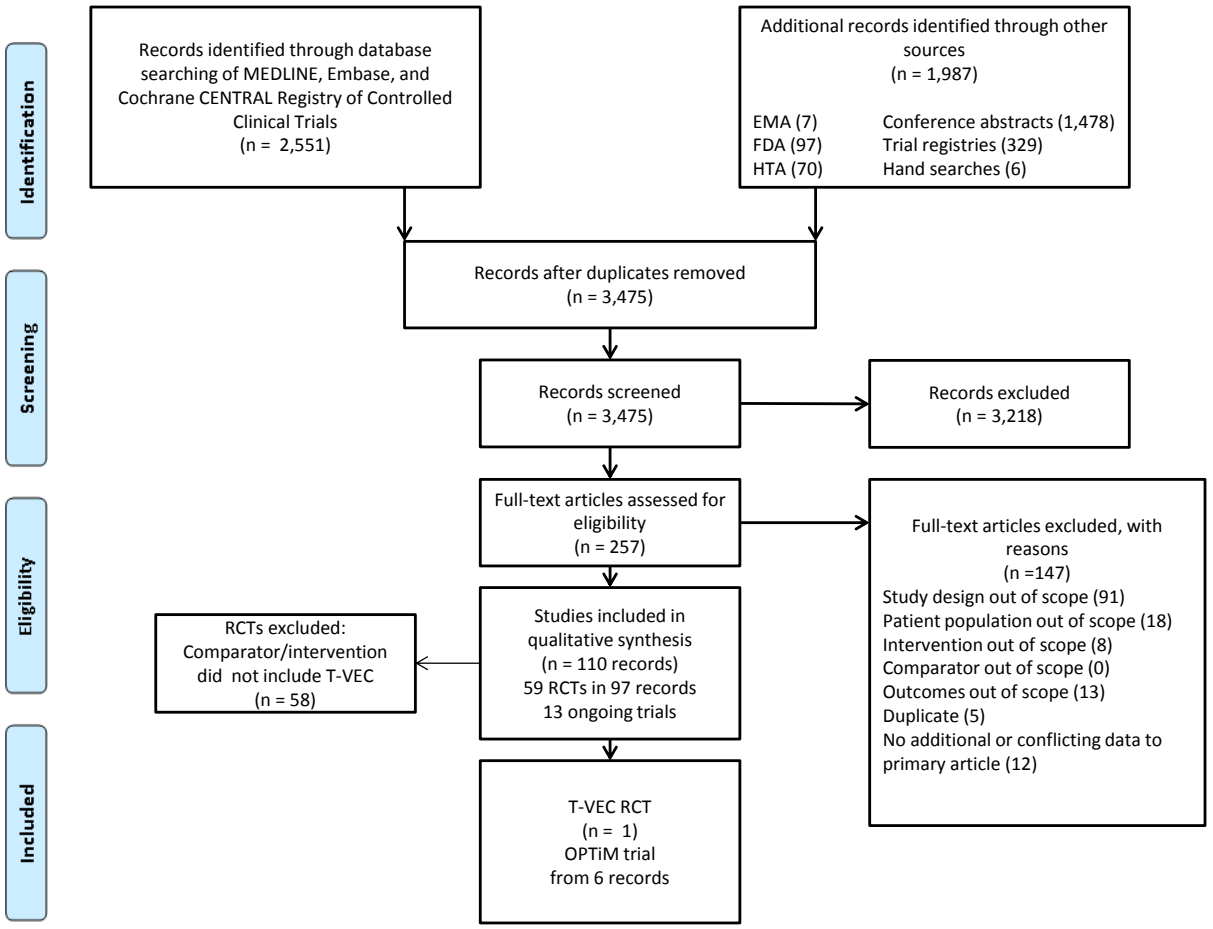
Abbreviations: HRQoL, health-related quality of life; RCT, randomised controlled trial; T-VEC, talimogene laherparepvec

In order to identify studies evaluating the intervention of interest, further exclusion criteria were applied to exclude any studies that did not assess T-VEC.

Study selection results for RCT evidence

Figure 4-1 presents the PRISMA flow diagram for the SLR. Prior to de-duplication 4,538 records were retrieved in total from electronic databases (n=2,551), rapid appraisal of other HTAs (n=70), EMA and FDA reports (n=104), conference abstracts (n=1,478), clinical trial registry records (n=329 records) and additional records identified from hand searching (n=6). After de-duplication, 3,475 titles and abstracts were screened by two reviewers independently for relevance according to the inclusion criteria for the review. Any discrepancies were resolved through consensus or consultation with a third reviewer. From these records, a total of 257 full-text records were obtained and screened in detail again by two independent reviewers, to determine whether they fulfilled the review inclusion criteria.
After subsequent detailed review, 97 records reporting data for 59 trials were selected as meeting all of the inclusion criteria and were extracted in full. In addition, there were 13 ongoing trials identified from the trial registry search. Only one relevant RCT evaluating T-VEC (i.e. OPTiM) was identified from the SLR.

Figure 4-1: PRISMA flow diagram for RCT evidence

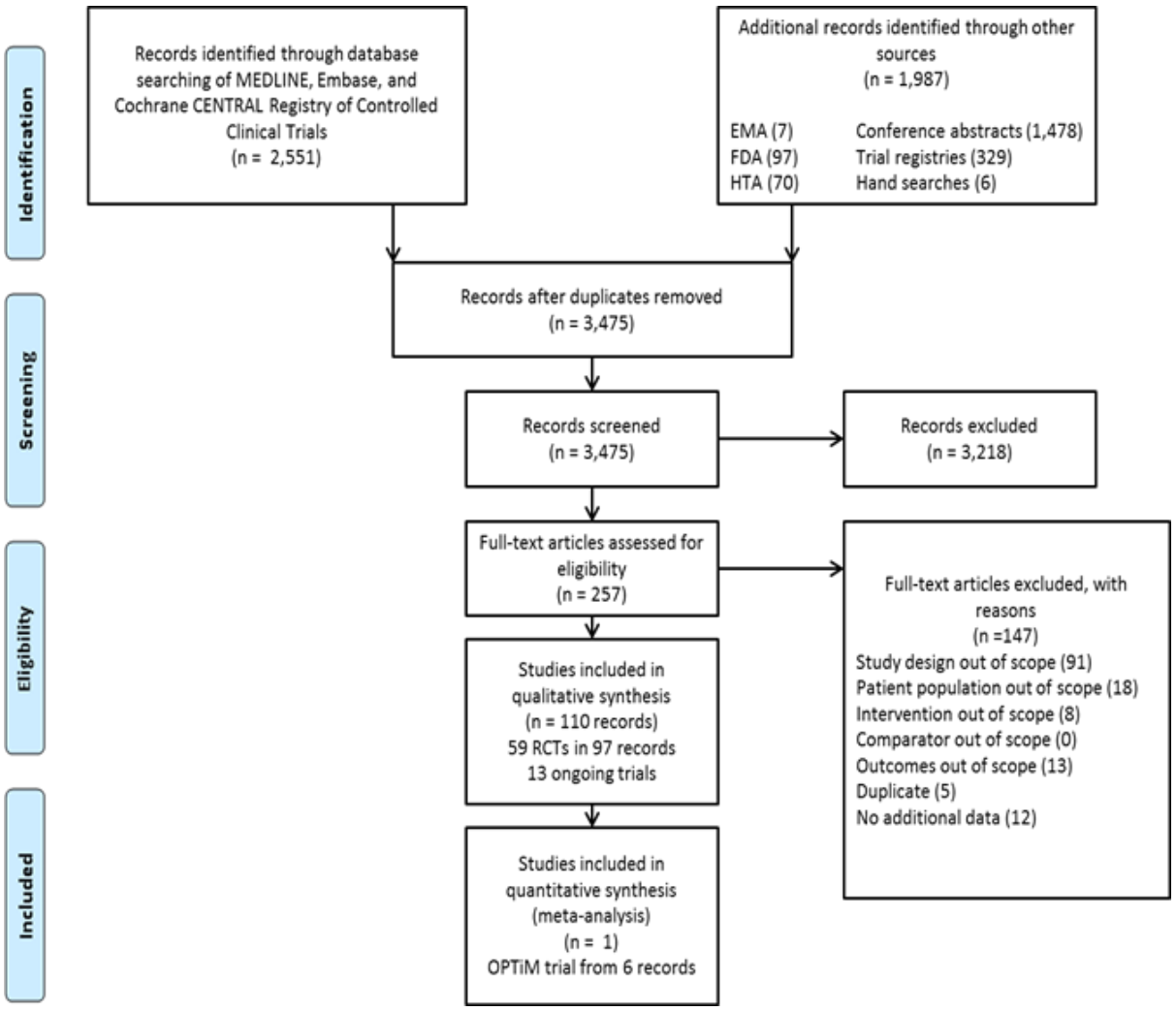


EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; RCT, randomised clinical trial

Study selection results for non-RCT evidence

Figure 4-2 presents the PRISMA flow diagram for the SLR for identification of relevant non-RCT evidence. Prior to de-duplication 5,169 records were retrieved in total from electronic databases (n=3,182), rapid appraisal of other HTAs (n=70), EMA and FDA reports (n=104), conference abstracts (n=1,478), clinical trial registry records (n=329 records) and additional records identified from hand searching (n=6). A total of 388 full-text articles were assessed for eligibility, from which 174 studies (in 178 records) were included in the qualitative synthesis. In addition, there were 13 ongoing trial identified from the trial registry search. Only one relevant non-RCT evaluating T-VEC was identified (i.e. study 002/03).

Figure 4-2: PRISMA flow diagram for non-RCT evidence



EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; RCT, randomised clinical trial; T-VEC, talimogene laherparepvec

4.2 List of relevant randomised controlled trials

The SLR identified one relevant phase III RCT assessing the safety and efficacy of T-VEC; the OPTiM study (005/05; NCT00769704)[79]. The comparator in the trial was GM-CSF and thus this study does not provide direct head-to-head evidence for any of the relevant comparators defined in the decision problem (Section 1.1). The comparative evidence for the

efficacy of T-VEC in metastatic melanoma versus treatments outlined in the decision problem is provided by the network meta-analysis presented in Section 4.10 and Section 4.11.

Although the OPTiM study included patients with stage IIIB-IV melanoma, the focus of this submission will be on patients with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease, in accordance with the anticipated marketing authorisation for T-VEC in the EU[4]. This was based on the observation during the OPTiM study that there was a larger clinical benefit in this group of patients with earlier disease[79]. A summary of the pivotal phase III OPTiM study can be seen in Table 4-2.

Table 4-2: Description of the relevant RCT - OPTiM

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
005/05; NCT00769704 (OPTiM)	Patients with injectable stage IIIB-IV melanoma that was not surgically resectable	T-VEC 10^8 pfu/mL administered via intralesional injection; administered 3 weeks after initial dose(10^6 pfu/mL) then once every 2 weeks Total injection volume was up to 4.0 mL per treatment session	GM-CSF 125 $\mu g/m^2$ once daily administered via subcutaneous injection for 14 days followed by 14 days of rest. Each cycle will be 28 days	Andtbacka R, *et al.* Journal of Clinical Oncology. 2015[79]
Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; RCT, randomised controlled trial; T-VEC, talimogene laherparepvec				

4.3 Summary of methodology of the relevant OPTiM RCT

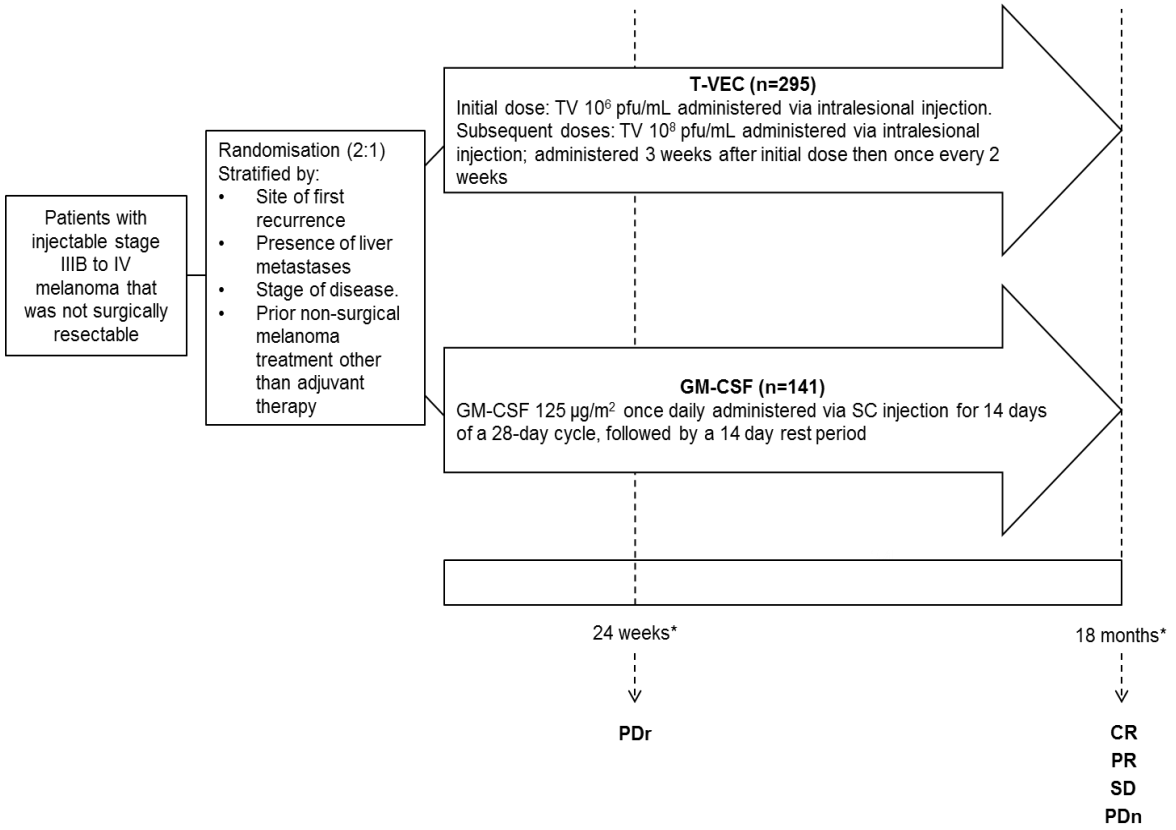
For the relevant RCT, OPTiM, a summary of trial design and methodology is presented in Table 4-3 and Figure 4-3, respectively.

The phase III OPTiM Study 005/05 was a randomised, multinational, clinical trial that compared T-VEC with subcutaneously administered GM-CSF in patients with stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable. Previous nonadjuvant systemic treatment for melanoma was allowed but not required. Patients were randomised in a 2:1 ratio to receive either T-VEC (n=295) or GM-CSF (n=141). The primary endpoint was durable response rate (DRR): partial response (PR) or CR that lasted continuously for ≥6 months. Responses were per modified World Health Organization (WHO) criteria by blinded central review. Key secondary endpoints included overall response rate (ORR) and OS[79]. Patients who had successfully completed treatment in the 12 month OPTiM study were eligible to enter into a 6 month extension study to assess the long-term safety and efficacy of T-VEC.

Selection of GM-CSF as the relevant comparator: At the time of study initiation, only high-dose aldesleukin (IL-2) and dacarbazine (DTIC) were licensed treatments for metastatic melanoma, with dacarbazine the most widely licensed in the range of study locations, including the UK. But since the study population included previously treated patients (approx. 50%), it was considered inappropriate to use dacarbazine and potentially re-treat patients with this therapy. At the time, GM-CSF represented a viable treatment for metastatic melanoma; with evidence of efficacy as an adjuvant therapy. It was also a biologically plausible comparator, being the product of the transgene expressed by T-VEC. Therefore it was important to exclude the possibility that the potential benefits of T-VEC could be obtained by administering GM-CSF alone. Finally, advice was sought from regulators, with agreement obtained from both UK (Medicines & Healthcare products Regulatory Agency [MHRA]) and US (FDA) authorities that GM-CSF was a suitable comparator.

The list of eligibility criteria and the description of OPTiM study endpoints are presented in Table 4-4 and Table 4-5.

Figure 4-3: OPTiM study design



Reference: OPTiM CSR[80]

* Subjects who did not experience clinically relevant disease progression at 24 weeks continued treatment for up to 18 months until response or criterion for withdrawal was met.

CR, complete response; GM-CSF, granulocyte macrophage colony-stimulating factor; PDr, clinically relevant disease progression; PDn, non-clinically relevant disease progression; PR, partial response; SC, subcutaneous; SD, stable disease; T-VEC, talimogene laherparepvec

Table 4-3: Summary of locations, trial design and methodology in the OPTiM study

Trial number (acronym)	**OPTiM (005/05; NCT00769704)**
Location	Canada, South Africa, **United Kingdom*** and United States
Trial design	Phase III, randomised allocation via IVRS, open-label, active-controlled 12-month study. Assignment was stratified by site of first recurrence, presence of liver metastases, disease stage, and prior nonadjuvant systemic treatment. Long-term extension study during which patients continued with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity
Eligibility criteria for participants	Patients with injectable stage IIIB-IV melanoma that was not surgically resectable Patients who had successfully completed treatment in the OPTiM 12 month study were eligible for inclusion in the long-term extension study if they did not have disease progression during the OPTiM study or had a CR but developed new lesions within 6 months
Settings and locations where the data were collected	The study was conducted at 64 centres across Canada, South Africa, **United Kingdom*** and United States and was overseen by an independent data monitoring committee (composed of multidisciplinary experts - two independent physicians and an independent biostatistician)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	**Intervention** T-VEC (N=295) ▪ Initial dose: T-VEC 10^6 pfu/mL administered via intralesional injection ▪ Subsequent doses: T-VEC 10^8 pfu/mL administered via intralesional injection; administered 3 weeks after initial dose then once every 2 weeks Total injection volume administered was up to 4.0 mL per treatment session. Injected volume per treatment session ranged from 0.1 mL to 4.0 mL depending on the size of lesions Dose modifications for T-VEC were not permitted. **Comparator** GM-CSF (N=141) ▪ GM-CSF 125 µg/m2 once daily administered via SC injection for 14 days of a 28-day cycle, followed by a 14 day rest period ▪ GM-CSF dose could be reduced by 50% for ANC>20,000/µl or platelet count >500,000/µl

Trial number (acronym)	OPTiM (005/05; NCT00769704)
Permitted and disallowed concomitant medication[80]	**Permitted medications (may be administered if needed, at the investigator's discretion, during the study:** ▪ Anti-emetics ▪ Anti-diarrhoeals ▪ Anti-allergic measures ▪ Palliative radiotherapy for pain caused by tumour lesions ▪ Erythropoietin, erythropoietin-like substances, blood or platelet transfusions ▪ Broad-spectrum antibiotics for suspected or documented infection are allowed according to local policy ▪ Bisphosphonate therapy is allowed according to local policy ▪ Topical anaesthetics at the injection site such as EMLA ▪ Intermittent topical acyclovir, but not permitted if it is to be applied within 20 cm of a T-VEC injection site ▪ Oral or systemic steroid medication use at a dose of ≤10mg/day of prednisone or equivalent (steroids with low systemic absorption (e.g. triamcinolone hexacetonide) injected into a joint space is allowed) ▪ Transient use of dexamethasone or a similar corticosteroid (i.e. no more than 1.5 mg dexamethasone) following stereotactic radiosurgery **Disallowed medications (not permitted during the study – treatment phase nor response evaluation):** ▪ Other investigational drugs ▪ Concomitant anti-tumour therapies other than radiation therapy required for palliation ▪ Oral or systemic steroids (with the exception of those used during the treatment for CNS disease) ▪ Anti-herpetic drugs, other than if topically administered >20 cm from a T-VEC injection site.
Primary outcomes	DRR, defined as the rate of CR + PR lasting ≥6 continuous months from the time the response was first observed and beginning within the first 12 months following treatment

Trial number (acronym)	OPTiM (005/05; NCT00769704)
Secondary/tertiary outcomes	**Efficacy** ▪ OS (key secondary endpoint) ▪ Overall response rate (ORR), complete response (CR) and partial response (PR) ▪ Response onset ▪ TTF ▪ Duration of response ▪ Risk of visceral and/or bone metastasis ▪ Evidence of local and systemic effects of T-VEC treatment **Safety** ▪ Safety was evaluated based on AEs, physical examinations and clinical laboratory assessment **HRQoL**
Scoring methods and timings of assessment	▪ Visible or palpable lesions were assessed by clinical evaluation (caliper or ruler). Deeper palpable lesions and non-palpable subcutaneous and distant metastatic lesions were assessed by whole-body CT, PET or PET-CT, and ultrasonography if appropriate ▪ Baseline and new tumours were observed, and response was assessed per modified WHO criteria. If a response was suspected to have occurred, confirmatory assessments were to be performed within 1 week. Patients with a best response per investigator of CR or PR or receiving treatment for ≥9 months were evaluated by a blinded EAC. Digital photography encompassing all visible disease was required for response assessment by EAC ▪ Clinical evaluation was performed at baseline and day 1 of each cycle; other assessments were performed at baseline and every 12 weeks ▪ AEs occurring from day 1 to 30 days after last treatment were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)
Pre-planned subgroups	Pre-planned subgroup analyses were conducted to investigate treatment effects across a number of covariates for various endpoints, including: ▪ Disease stage (IIIB/IIIC vs IVM1a vs IVM1b vs IVM1c) ▪ Line of therapy (first- vs second-line or greater) ▪ Gender (male vs female)

Trial number (acronym)	OPTiM (005/05; NCT00769704)
	▪ ECOG performance status (0 vs 1) ▪ HSV-1 status (negative vs positive)
Duration of follow-up	36 months from the date the last patient was randomised or until the last patients has died, whichever is earlier Patients in the extension study were allowed to continue with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity.

References: Andtbacka et al[79]; OPTiM[80]

* **There were 9 study sites in the UK (one each in Birmingham, Cambridge, Leicester, Leeds, Oxford and Southampton and three in London)**

ANC, absolute neutrophil count; AE, adverse event; CNS, central nervous system; CR, complete response; CSR, clinical study report; CT, computed tomography; DRR, durable response rate; EAC, Endpoint Assessment Committee; ECOG, Eastern Cooperative Oncology Group; EMLA, eutectic mixture of local anaesthetics; GM-CSF, granulocyte macrophage colony-stimulating factor; HRQoL, health-related quality of life; HSV-1, herpes simplex virus type 1; IVRS, interactive voice response system; OS, overall survival; PET, positron emission tomography; PR, partial response; pfu, plaque forming units; SC, subcutaneous; TTF, time to treatment failure; T-VEC, talimogene laherparepvec; WHO, World Health Organisation

Table 4-4: Summary of eligibility criteria in the OPTiM study

Study (Acronym)	Inclusion criteria	Exclusion criteria
005/05; NCT00769704 (OPTiM)	▪ Males or females age ≥18 years ▪ Histologically confirmed diagnosis of malignant melanoma ▪ Stage IIIB-IV disease that is not surgically resectable ▪ Measurable disease defined as: o at least one melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the greatest ,diameter is ≥10 mm as measured by contrast-enhanced or spiral CT scan for visceral or nodal/soft tissue disease (including lymph nodes) and/or; o at least one ≥10 mm superficial cutaneous melanoma lesion as measured by callipers and/or; o at least one ≥10 mm subcutaneous melanoma lesion and/or; o multiple superficial melanoma lesions which in aggregate have a total diameter of ≥10 mm. ▪ Injectable disease (i.e. suitable for direct injection or through the use of ultrasound guidance) defined as: o at least one injectable cutaneous, subcutaneous or nodal melanoma lesion ≥10 mm in longest diameter or; o multiple injectable melanoma lesions which in aggregate have a longest diameter of ≥10 mm ▪ Serum LDH levels ≤1.5 x ULN ▪ ECOG performance status of 0 or 1 ▪ Life expectancy >4 months from the date of randomisation ▪ Provide written informed consent in accordance with all applicable regulations and follow the study procedures. Patients must be capable of understanding the investigational	▪ Clinically active cerebral or any bone metastases. Patients with up to 3 (neurological performance status of 0) cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, gammaknife therapy, with no evidence of progression, and have not required steroids, for at least 2 months prior to randomisation ▪ >3 visceral metastases (this does not include lung metastases or nodal metastases associated with visceral organs). For patients with ≤3 visceral metastases, no lesion >3 cm, and liver lesions must meet RECIST criteria for SD for at least 1 month prior to randomisation ▪ Any underlying medical condition, which in the opinion of the investigator, would make administration of the study drugs hazardous or make it difficult to monitor adverse effects ▪ History of second cancer unless disease-free for >5 years. In the case of malignancies that are diagnosed at a stage where a definitive therapy results in near certain cure, a disease free interval of <5 years is permissible. The Medical Monitor must approve such patients ▪ Primary ocular or mucosal melanoma ▪ Evidence of immunosuppression for any reason: o known HIV disease o acute or chronic active hepatitis B or hepatitis C infection o chronic oral or systemic steroid medication use at a dose of >10 mg/day of prednisone or equivalent (steroids with low systemic absorption [e.g. triamcinolone hexacetonide] injected into a joint space is allowed) o other signs or symptoms of clinical immune system suppression ▪ Baseline prolongation of QT/QTc interval (QTc interval >470 msec) ▪ Open herpetic skin lesions

Study (Acronym)	Inclusion criteria	Exclusion criteria
	nature, potential risks and benefits of the study ▪ Adequate organ function determined within 4 weeks prior to randomisation, defined as: o ANC ≥1500/mm^3 o platelet count ≥100,000/mm^3 o haemoglobin ≥8 g/dL without need for haematopoietic growth factor or transfusion support o serum creatinine ≤1.5 x ULN, or 24-hour creatinine clearance ≥50 cc/min. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits) o serum bilirubin ≤1.5 x ULN o AST ≤2.5 x ULN o ALT <2.5 x ULN o alkaline phosphatase ≤2.5 x ULN o serum albumin ≥2.5 g/dL o PT ≤1.5 x ULN (or INR ≤1.3)* o PTT ≤1.5 x ULN*	▪ Pregnant or breast-feeding female. Confirmation that women of child-bearing potential are not pregnant. A negative serum or urine β-hCG pregnancy test result must be obtained during the screening period ▪ Fertile males and females who are unwilling to employ adequate means of contraception (e.g. condom with spermicide, diaphragm with spermicide, birth control pills, injections, patches, or intrauterine device) during study treatment and through 30 days after the last dose of study treatment ▪ Previous treatment with T-VEC or treatment with GM-CSF for active disease (prior adjuvant therapy with GM-CSF is permitted) ▪ Currently enrolled in another clinical research study or received an investigational agent for any reason within 4 weeks prior to randomisation ▪ Require intermittent or chronic treatment with an anti-herpetic drug (e.g. acyclovir), other than intermittent topical use

References: Andtbacka et al[79]; OPTiM[80]

* Prolongation in INR, PT, and PTT when the result is from therapeutic anticoagulation treatment are permitted for patients whose injectable lesions are cutaneous and/or subcutaneous such that direct pressure could be applied in the event of excessive bleeding.

ALT, alanine amino transferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating factor; HIV, human immunodeficiency virus; INR, international normalised ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; T-VEC, talimogene laherparepvec; ULN, upper limit of normal

Table 4-5: Summary of key endpoints and assessments in the OPTiM study

Endpoint	Definition	Assessed by
Primary endpoint		
DRR	The percentage of patients with CR or PR maintained continuously for at least 6 months (183 days) from when an objective response was first observed and initiating at any point within 12 months of starting therapy. This reflects all new sites of disease as well as disease sites identified at baseline	EAC and investigator
Secondary endpoints		
OS	The time from the date of randomisation to the date of death from any cause. Death was the event of interest. OS time was censored at the last date the patient was known to be alive when the confirmation of death was absent or unknown. Patients were censored at the date of randomisation if no additional follow-up data was obtained	Investigator
Best overall response and tumour burden	Best overall response observed across all time points. Disease burden at a particular assessment time was defined as the sum of the products of the perpendicular diameters of all measurable tumours identified at baseline plus the sum of the products of the perpendicular diameters of all measurable new lesions that appeared since baseline	EAC and investigator
Response onset	The time from the date of randomisation to the date of the first documented evidence of response. This may have extended beyond the planned study duration for however long the patient was followed. The achievement of response was the event of interest. If no response was observed, response onset was censored at the last tumour assessment date or at the time of the new anti-cancer therapy, whichever was earlier. In the event that there was one or more missed or partially missing assessments for response and the next assessment showed response, the patient should have been scored as response on the first date when complete information was available to declare response	Investigator
TTF	Calculated from baseline until the first clinically relevant disease progression (PDr) where there is no response achieved after the PDr. PDr is the event of interest. The TTF was subject to censoring at the last tumour assessment if the patient had not yet experienced PDr. In the event that there was one missed or partially missing assessment for PDr and the next assessment showed PDr, the patient should have been scored as PDr on the visit showing PDr. If there was PDr following two or more missed assessments, the patient should have been censored at the time of the last tumour assessment before PDr	Investigator
Duration of response	The longest individual period from entering response (PR or CR) to the first documented evidence of the patient no longer meeting the criteria for being in response or death, whichever was earlier. The duration of response was defined to be zero if no PR or CR was ever achieved. This allowed all responders and non-responders to be included in the calculations. If the patient was last reported to be either a PR or CR, the duration of response was subject to censoring at that point	Investigator

Endpoint	Definition	Assessed by
Response interval	Defined as the time from the date of randomisation to the date of the last documented evidence of response prior to any new anti-cancer therapy which may be given. Response interval will be zero if no response was ever achieved. This allows all randomised patients to be included in the analysis but post onset of response will be censored if the patient is still in response at the last observation, which may extend beyond the planned study duration for however long the patient is followed	Investigator
Safety endpoints		
Safety	Assessments for safety included all randomised and treated patients. Patients who were randomised but withdrew from the trial before receiving any study treatment were excluded from the safety assessment, but were still followed for response and survival. Safety assessments were based on AEs, laboratory data, concomitant medications, the results of physical examinations and vital signs. Safety was evaluated using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0, based on recorded AEs, physical examinations, and clinical laboratory assessments. All AEs were coded according to Medical Dictionary for Regulatory Activities version 10.1 or later. If a patient experienced multiple events that map to a single AE, the greatest severity and strongest Investigator assessment of relation to study drug was assigned to the AE in order to summarise the findings for the purpose of comparing T-VEC and GM-CSF	Investigator
Exploratory endpoints		
Quality of life	To assess patient reported quality of life in patients treated with T-VEC and GM-CSF with a standardised instrument, the Functional Assessment of Cancer Therapy-biological response modifier (FACT-BRM) was used	Investigator
Impact of response and durable response on survival	The relationship between achieving a response and a durable response and subsequent survival prolongation was explored	Investigator
Influence of BRAF mutation status	Where information is available, exploratory analysis of treatment effects based on BRAF mutation status may be conducted	Investigator

Reference: OPTiM[80]

AE, adverse event; CR, complete response; DRR, durable response rate; GM-CSF, granulocyte macrophage colony-stimulating factor; OS, overall survival; PDr, clinically relevant disease progression; PFS, progression-free survival; PR, partial response; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

4.4 Statistical analysis and definition of study groups in the relevant OPTiM RCT

An overview of the primary hypothesis, statistical tests used in the primary analysis, power of the trial (including description of sample size calculation with rationale and assumptions), and data management for each of the relevant RCTs is provided in Table 4-6.

The planned population size in the OPTiM study was 430 patients, assigned in a 2:1 ratio to treatment with T-VEC or GM-CSF, respectively. This provided 95% and 90% power for a two-sided α 0.05 using Fisher's exact test in the intent-to-treat and per-protocol populations, respectively, to detect an estimated DRR difference of 13% versus 3%)[79].

Planned interim analyses included:

- Assessment of safety after 20 patients had received 8 doses of T-VEC,
- Assessment of DRR after 75 patients had been on the study for nine months to assess safety and efficacy on the basis of both ORR and DRR,
- Assessment of DRR after all patients were randomly assigned.

Primary analysis of DRR was planned when no additional patients had the possibility of meeting the criteria for durable response, at which time, on a positive result, an interim analysis of OS was planned after 250 events. OS was tested with an unadjusted log-rank test conditional on a statistically significant difference in DRR. Primary analysis of OS required at least 290 events with 90% power to detect a HR of 0.67 with two-sided of 0.05, without adjustment for interim analysis. The final, descriptive analysis of OS was planned when all subjects had been followed for at least 3 years after randomization.

Table 4-6: Summary of statistical analyses in the RCTs

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
OPTiM study	The null hypothesis was that there was no difference in DRR between the T-VEC and control arms at the interim or final analysis	Primary efficacy analyses were based on the ITT population. Safety analyses included patients who received at least one dose of T-VEC or GM-CSF Primary analysis of DRR (with one-sided type I error rate of 0.0244) was planned when no additional patients had the possibility of meeting the criteria for durable response OS was tested with an unadjusted log-rank test conditional on a statistically significant difference in DRR. Primary analysis of OS required at least 290 events with 90% power to detect a HR of 0.67 with two-sided α of 0.05, without adjustment for interim analysis The final, descriptive analysis of OS was planned when all subjects had been followed for at least 3 years after randomization Difference in DRR per EAC between treatment arms was evaluated using an unadjusted Fisher's exact test. OS, TTF, time to response, and duration of response were evaluated using unadjusted log-rank tests and Cox proportional hazards models	The planned population was 430 patients (randomly assigned 2:1). This provided 95% and 90% power for a two-sided α of 0.05 using Fisher's exact test in the ITT and PP populations, respectively, to detect an estimated DRR difference of 13% vs 3%	If one or more radiographic assessments are missing, the most recent date that a response was documented will be used as the date of response. The date of response onset was defined as the first date when complete information was available to declare response For duration of response, if progression was not documented, then the date of death was be defined as the date of progression in the event that the patient died If a patient withdrew from treatment before PD, they were to return for the end of treatment/early termination visit and then undergo long-term follow-up every 3 months to assess survival until end of study (i.e. 36 months from the date the last patient enrolled was randomised, or until the last patient died, whichever was the earlier)

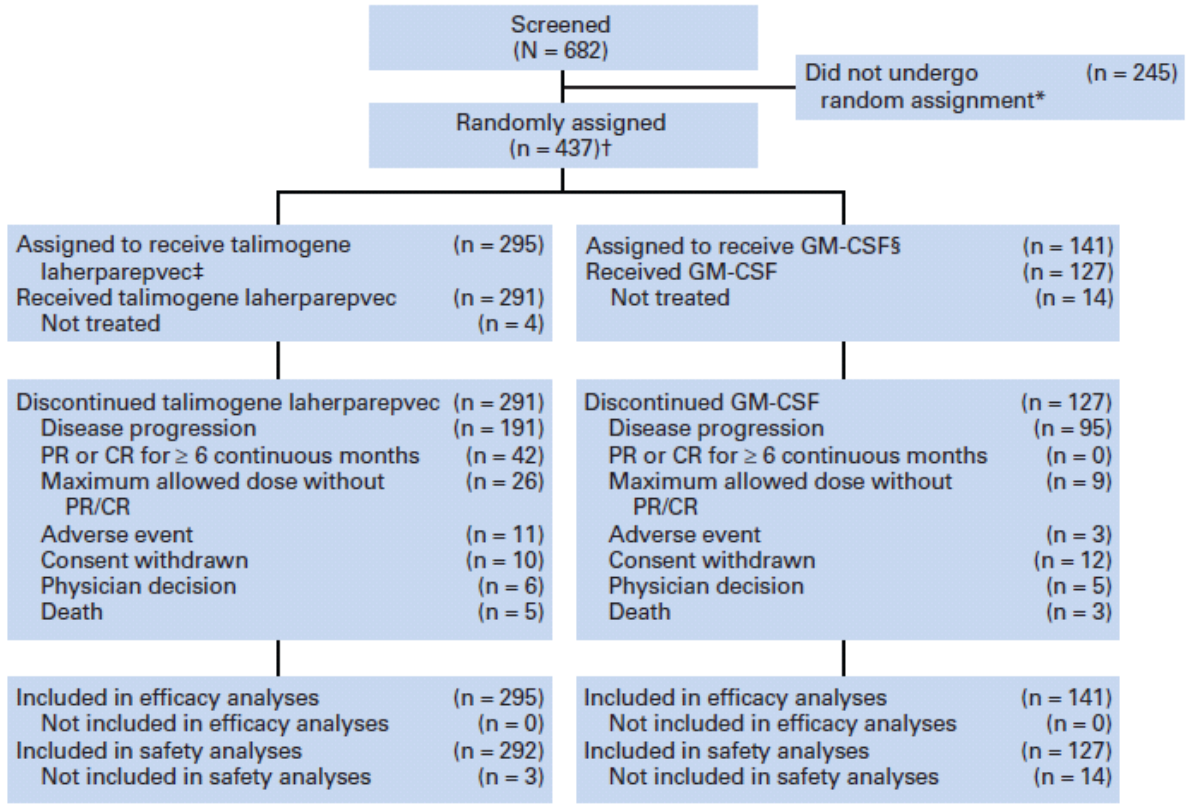
References: Andtbacka et al[79]; OPTiM[80]

DRR, durable response rate; EAC, endpoint assessment committee; GM-CSF, granulocyte macrophage colony-stimulating factor; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD, progressive disease; PP, per-protocol; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

4.5 Participant flow in the relevant OPTiM RCT

The OPTiM ITT population consisted of 436 patients who were randomised to treatment with T-VEC (N=295) or GM-CSF (N=141). Patient disposition during OPTiM for the ITT population is shown in Figure 4-4[79].

Figure 4-4: Patient disposition during the OPTiM study



Reference: Andtbacka et al 2015[79]

CR, complete response; GM-CSF, granulocyte macrophage colony-stimulating factor; PR, prolonged response

* includes patients who were screened but did not meet eligibility criteria. 26 patients in T-VEC arm (9%) and 7 in GM-CSF arm (5%) were enrolled and randomly assigned but had at least one inclusion or exclusion criteria Violation

† there were 439 random assignments; however, one patient was later determined to have been randomly assigned three times at three different sites and was excluded from the ITT analysis set (i.e. N=436) but was included in the safety analysis set (N=437). The patient ultimately received T-VEC after two initial random assignments to GM-CSF

‡ T-VEC was administered intralesionally ≤ 4 mL x 10^6 pfu/mL once and, after 3 weeks, ≤ 4 mL x10^8 pfu/mL every 2 weeks

§ GM-CSF 125 μg/m2 subcutaneously for 14 days in 4-week cycles

At time of analysis of the primary data cut, all patients had discontinued study treatment in the main protocol but could have enrolled onto a treatment extension study if appropriate. Median duration of treatment in the T-VEC and GM-CSF arms was 23.0 weeks (range, 0.1 to 78.9 weeks) and 10.0 weeks (range, 0.6 to 72.0 weeks), respectively. Median potential follow-up (time from random assignment to analysis) was 44.4 months (range, 32.4 to 58.7 months) at the primary analysis of OS.

A total of 31 patients (28 treated with T-VEC and 3 treated with GM-CSF) of the 436 patients from the OPTiM study entered the extension trial. Including treatment received in the OPTiM study, median treatment duration was 88 weeks (range: 29-177 weeks) for T-VEC and 100 weeks for GM-CSF (range: 54-120 weeks). Patients who entered the extension trial were included in both the analysis for the primary and final data cut-off[80, 81].

Disposition of patients in the IIIB-IVM1a disease population and the ITT population in the OPTiM study are presented in Table 4-7. Patient dispositions were similar for the overall study population and those with no visceral disease (stages IIIB-IVM1a), except that the rate of patients who discontinued the study treatment was smaller in patients without visceral disease, particularly in the T-VEC arm.

Table 4-7: Summary of patient disposition in the OPTiM study

	Disease stage			
	IIIB–IVM1a (T-VEC label population)		IIIB–M1c (ITT population)	
	T-VEC	GM-CSF	T-VEC	GM-CSF
Efficacy population, n	163	86	295	141
Discontinued from treatment, n (%)	162 (99.4)	76 (88.4)	291 (98.6)	127 (90.1)
Discontinued from study, n (%)	67 (41.1)	57 (66.3)	168 (56.9)	99 (70.2)
Median duration on study, months	23.3	19.3	20.6	18.5
Stratification factors	n/a	n/a	• Site of first recurrence • Stage of disease • Presence of liver metastases • Prior nonsurgical melanoma treatment other than therapy	

Reference: Amgen 2015 data on file[80] _ENREF_83

GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent to treat; T-VEC, talimogene laherparepvec

Baseline Patient Characteristics

Of the 436 patients included in the OPTiM ITT population, a total of 249 (57%) patients had stage IIIB-IVM1a disease and 47% had not received prior systemic therapy for metastatic disease. Baseline characteristics for the overall patient population and the stage IIIB-IVM1a population were similar Table 4-8. In the stage IIIB-IVM1a population baseline characteristics including sex, age, line of therapy and HSV serostatus were generally balanced across the two treatment groups. However, there was a slight imbalance between the proportion of patients with Eastern Cooperative Oncology Group (ECOG) status of 0 (74% vs 63% for patients in the T-VEC and GM-CSF treatment groups, respectively)[80] _ENREF_83

Table 4-8: Baseline characteristics of participants in the OPTiM study

Characteristic	IIIB–IVM1a (T-VEC label population)		IIIB–IVM1c (ITT)	
	T-VEC (N=163)	GM-CSF (N=86)	T-VEC (N=295)	GM-CSF (N=141)
Age (median/ mean)	63.0/64.5	62.5/62.5	63.0/63.1	64.0/62.9
Female, n (%)	71 (43.6)	39 (45.3)	122 (41.4)	64 (45.4)
ECOG, n (%)				
0	120 (73.6)	54 (62.8)	209 (70.8)	97 (68.8)
1	42 (25.8)	24 (27.9)	82 (27.8)	32 (22.7)
Missing	1 (0.6)	8 (9.3)	4 (1.4)	12 (8.5)
Disease stage from CRF, n (%)				
Stage IIIB	22 (13.5)	12 (14.0)	22 (7.5)	12 (8.5)
Stage IIIC	66 (40.5)	31 (36.0)	66 (22.4)	31 (22.0)
Stage IVM1a	75 (46.0)	43 (50.0)	75 (25.4)	43 (30.5)
Stage IVM1b	0 (0.0)	0 (0.0)	64 (21.7)	26 (18.4)
Stage IVM1c	0 (0.0)	0 (0.0)	67 (22.7)	29 (20.6)
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0)
LDH, n (%)				
≤ULN	154 (94.5)	75 (87.2)	266 (90.2)	124 (87.9)
>ULN	2 (1.2)	2 (2.3)	15 (5.1)	5 (3.5)
Unknown	7 (4.3)	9 (10.5)	14 (4.7)	12 (8.5)
Prior nonsurgical procedures from CRF, n (%)				
Yes	104 (63.8)	51 (59.3)	202 (68.5)	89 (63.1)
No	53 (32.5)	24 (27.9)	80 (27.1)	36 (25.5)
Unknown	6 (3.7)	11 (12.8)	13 (4.4)	16 (11.3)

Reference: Amgen data on file[80]

CRF, case report form; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte–macrophage colony-stimulating factor; LDH, lactate dehydrogenase; ULN, upper limit of normal; T-VEC, talimogene laherparepvec

Treatment exposure

In the subgroup of patients with stage IIIB-IVM1a disease, the median duration of treatment with T-VEC was more than double that of GM-CSF. The median duration of treatment was 26 weeks (range: 4 weeks to 79 weeks) in the T-VEC treatment group compared with 10 weeks (range:1 week to 58 weeks) in the GM-CSF treatment group (Table 4-9). The median initial dose of T-VEC was 3.00mL ($x10^6$ pfu) (range: 0.5mL to 4.0mL) and median subsequent dose of T-VEC was 2.76mL ($x10^8$ pfu) (range: 0.3mL to 4.4 mL). The median cumulative volume of T-VEC administered over the treatment duration was 27.2mL (range: 2.5mL to 135.0mL) with a median of 14.0 injections (range: 2 to 38 injections (Table 4-9)[80].[80]

Table 4-9: Summary of treatment exposure in patients with stage IIIB-IVM1a disease (safety population)

	Patients with stage IIIB-IVM1a disease	
	T-VEC (N=163)	**GM-CSF (N=76)**
Treatment duration (weeks)		
Mean	30	15
Median	26	10
Min-Max	4-79	1-58
Dose at cycle one, day one (mL)		
Mean	2.69	-
Median	3.00	-
Min-Max	0.5-4.0	-
Average dose volume post cycle one, day one (mL)		
Mean	2.60	-
Median	2.79	-
Min-Max	0.3-4.4	-
Cumulative volume (mL)		
Mean	37.04	-
Median	27.20	-
Min-Max	2.5-135.0	-
Number of injections		
Mean	15.4	-
Median	14.0	-
Min-Max	2-38	-

Reference: Amgen data on file[80]

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

Subsequent treatment in patients with stage IIIB-IVM1a disease

Further treatments administered to patients enrolled in the OPTiM study are detailed in Table 4-10.

Table 4-10: Summary of selected subsequent therapies given to patients following participation in the OPTiM study

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)	63 (44.7)	119 (40.3)
Ipilimumab	61 (37.4)	32 (37.2)	49 (34.8)	106 (35.9)
Vemurafenib	15 (9.2)	13 (15.1)	21 (14.9)	27 (9.2)
Dabrafenib	6 (3.7)	2 (2.3)	2 (1.4)	7 (2.4)
Trametinib	3 (1.8)	0 (0.0)	0 (0.0)	3 (1.0)
Anti-PD1 antibody	2 (1.2)	4 (4.7)	4 (2.8)	5 (1.7)

Reference: OPTiM[80]; Harrington et al 2015[82]

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

4.6 Quality assessment of the relevant OPTiM RCT

In order to assess the risk of bias and generalisability of the OPTiM study, quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)'[83].

Critical appraisal of the OPTiM study has been summarised in Table 4-11. Overall, randomisation and concealment of treatment allocation during the OPTiM study was appropriately conducted via use of an interactive voice response system. Moreover, the risk of bias from the open-label study design was mitigated by the fact that the data for the primary endpoint – DRR – were reviewed and confirmed by an independent and blinded endpoint assessment committee.

Table 4-11: Quality assessment results for the OPTiM study

Study question	Further details on how the question is addressed in the study	Short response
Was randomisation carried out appropriately?	Patients were randomised to T-VEC or GM-CSF in a 2:1 allocation, and were assigned a subject number and treatment arm through a central randomisation system with telephone access – i.e. an IVRS with a fixed key size appropriate for a 2:1 allocation. Randomisation was stratified by known prognostic factors: site of first recurrence; presence of liver metastases; stage of disease; prior nonadjuvant systemic treatment	Yes
Was the concealment of treatment allocation adequate?	Allocation to a treatment arm in the OPTiM study was through a central system and an IVRS	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	During the study, treatment arms were broadly balanced for randomisation covariates (i.e. proportions were within 2% of each other in study arms). However there were some small imbalances (i.e. greater than 5%) for certain non-randomisation prognostic covariates. Specifically, there were 5%, 6%, 9% and 7% more patients in the GM-CSF arm with stage IVM1a disease, stage IIIB-IVM1a disease, absence of visceral disease and unknown ECOG performance status, respectively than in the T-VEC arm. Similarly there were 5%, 9% and 5% more patients with stage IVM1b-c disease, visceral disease, and with ECOG performance status 1, respectively in the T-VEC arm than the GM-CSF arm	No
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study. However, the data for the primary endpoint – DRR – were reviewed and confirmed by an independent, blinded EAC Assessment of OS was not affected by the study design. It is acknowledged that the open-label study design may have influenced assessment of time to treatment failure	N/A
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected differences in drop-outs between the two randomised treatment arms of the study were reported	No

Study question	Further details on how the question is addressed in the study	Short response
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest that the study authors measured more outcomes than they reported	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were based on the ITT population. This was defined as all subjects who were randomised once to study treatment. Missing or uninterpretable data were resolved by the study investigator and logged in case report forms. With respect to assessment of the primary endpoint (DRR) of the OPTiM study, the EAC was permitted to employ last value carry forward imputation to account for missing lesion assessments to determine if treatment response is maintained or terminated	Yes

References: Andtbacka et al[79]; OPTiM[80]

DRR, durable response rate; EAC, endpoint assessment committee; ECOG; Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent to treat; IVRS = interactive voice response system; OS, overall survival; T-VEC, talimogene laherparepvec

4.7 Efficacy results of the relevant OPTiM RCT

All pre-specified primary, secondary, and tertiary efficacy outcomes for the OPTiM study were reported for the ITT population of adults with unresectable stage IIIB-IV melanoma[79].

Results showed that among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; P .001). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P =.051).

However, in accordance with the expected marketing authorisation for T-VEC in the EU[4], only data for patients with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (i.e. stage IIIB-IVM1a) are presented in the main section of the submission (data for the full ITT population is presented in Appendix 1.3). Table 4-12 summarises details of outcomes and analyses presented within the results section.

Table 4-12: Details of RCT evidence presented for relevant OPTiM RCT

Population and data cut	Outcomes presented in main submission
Patients with stage IIIB-IVM1a Primary data cut – 31st March 2014 Final data cut – 8th August 2014	• Durable response rate (DRR) – primary endpoint • Overall survival (OS) – key secondary endpoint • Response rates: Overall response rate (ORR), complete response rate (CRR) and partial response rate (PRR) • Response onset • Time to treatment failure (TTF) • Duration of response • Risk of visceral and/or bone metastasis (post hoc analysis) • Evidence of Local and Systemic Effects of T-VEC Treatment
Reference: Andtbacka et al 2015[79]	
CRR, complete response rate; DRR, durable response rate; ORR, overall response rate; OS, overall survival; PRR, partial response rate; TTF, time to treatment failure	

Primary endpoint

Durable Response Rate (per EAC assessment)

DRR at the primary and final data cuts based on EAC assessment in patients with stage IIIB-IVM1a disease in the OPTiM study are shown in Table 4-13.

For both analyses, treatment with T-VEC resulted in an improvement in DRR compared with GM-CSF (25.2% vs 1.2%; unadjusted OR 28.6; 95% CI: 3.9, 211.5; P<0.0001;)[80]. This finding was consistent with the treatment benefit observed in the ITT population (Appendix 1.4)[79]. Among patients who achieved a DR, the survival rate at 3 years was 95% and at 4 years was 87% (Figure 4-5). In addition to improved OS, achieving DR was associated with reduced risk of initiating subsequent systemic therapy: HR (DR vs no DR) = 0.33 (95% CI:

0.17-0.65), P=0.0007 and patients with a DR had a higher quality of life improvement rates versus patients with no DR: odds ratio (DR vs no DR) = 2.8 (95% CI: 1.1-7.0), P=0.0247.

Table 4-13: DRR based on EAC assessment in patients with stage IIIB-IVM1a disease

	T-VEC (n=163)	GM-CSF (n=86)	Treatment difference (T-VEC/GM-CSF)
Primary data cut			
DRR based on EAC, n (%)	41 (25.2)	1 (1.2)	40 (24.0)
95% CI[a]	(18.5, 31.8)	(0.0, 3.4)	(17.0, 31.0)
Unadjusted p-value[b]	–	–	<0.0001
Unadjusted odds ratio (T-VEC/GM-CSF)[c]	–	–	28.6
95% CI[c]	–	–	(3.9, 211.5)
Final data cut			
DRR based on EAC, n (%)	41 (25.2)	1 (1.2)	40 (24.0)
95% CI[a]	(18.7, 32.5)	(0.0, 6.3)	(15.2, 31.6)
Unadjusted p-value[b]			<0.0001
Unadjusted odds ratio (T-VEC/GM-CSF)[c]			28.6
95% CI[c]			(3.9, 211.5)

References: Harrington 2015[82]; Amgen data on file[80]

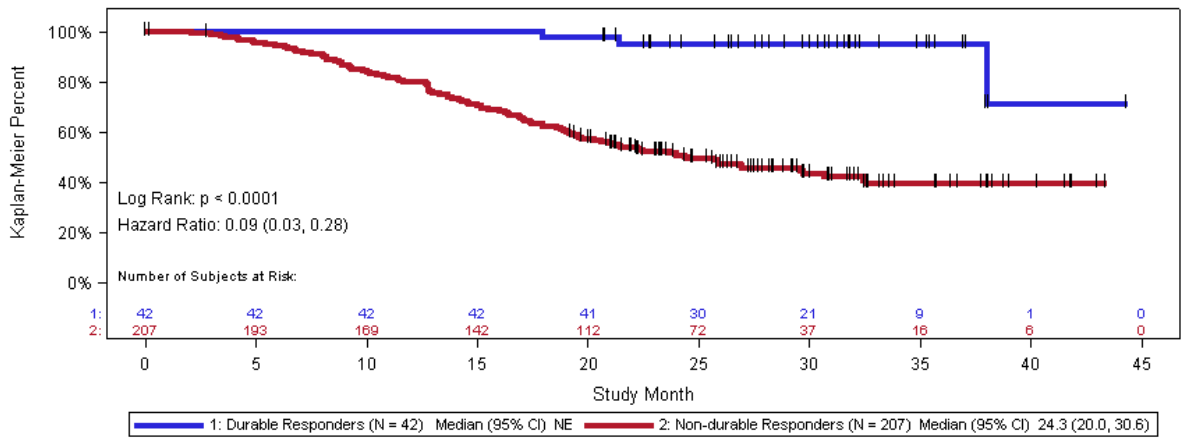
[a] The Clopper-Pearson method was used to calculate exact CIs for binary endpoints. Wilson's score method with continuity correction was used to calculate an approximate CI for between-group differences in binary rates

[b] Using Fisher's Exact Test

[c] Obtained from a logistic regression model with logit link. An odds ratio >1.0 indicates a higher DRR for T-VEC relative to GM-CSF

CI, confidence interval; DRR, durable response rate; EAC, Endpoint Assessment Committee; GM-CSF, granulocyte macrophage colony-stimulating factor T-VEC, talimogene laherparepvec

Figure 4-5: Kaplan-Meier plot of OS by durable response in per EAC in Stage IIIB, IIIC, and IVM1a patients with no visceral disease



Subjects that have not been recorded as dead are included as censored

ITT population includes ass subjects who have been randomised to receive study treatment. OS is calculated as the number of months from randomisation date to death date or last known to be alive date

CI, confidence interval; NE, non-estimable; OS, overall survival

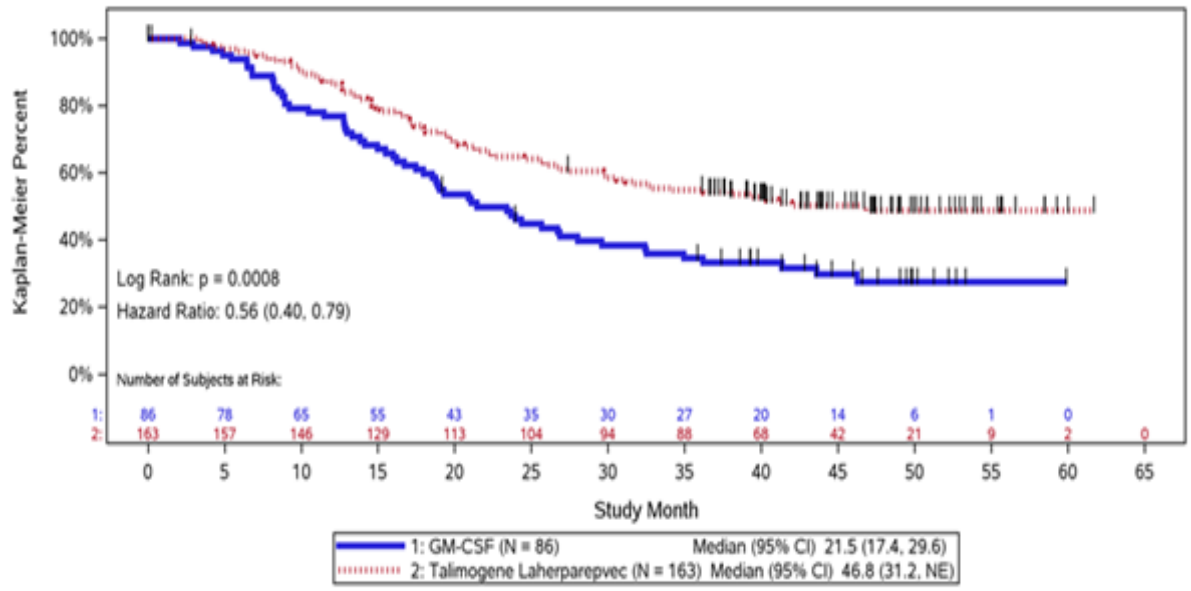
Secondary endpoints

Overall survival (OS)

OS results at both the primary and final OS data cuts are presented in Table 4-14. In the primary OS data cut, a 19.6 month improvement in median OS was observed in patients treated with T-VEC compared with patients treated with GM-CSF (median OS: 41.1 months versus 21.5 months, respectively; HR 0.57; 95% CI: 0.40, 0.80; p=0.0009)[84].

Similar results were observed in the final, descriptive data cut of OS (conducted when all subjects had been followed for at least three years after randomisation). A median OS improvement of 25.3 months was observed in patients treated with T-VEC compared with patients treated with GM-CSF (median OS: 46.8 months versus 21.5 months, respectively; unstratified HR 0.56; 95% CI: 0.40, 0.79; p=0.0008) (Figure 4-6; Table 4-14)[80].

Figure 4-6: Kaplan Meier curves for OS in patients with stage IIIB-IVM1a disease – final data cut



Reference: Amgen data on file[80]
CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; NE, non-estimable; OS, overall survival

In the ITT population, median OS was longer in patients treated with T-VEC compared with patients treated with GM-CSF for both the primary and final data cuts (Appendix 1.3).

Table 4-14: OS in patients with stage IIIB-IVM1a disease

	T-VEC (n=163)	**GM-CSF (n=86)**
Primary OS data cut		
Subject status, n (%)		
Deaths	80 (49.1)	57 (66.3)

	T-VEC (n=163)	GM-CSF (n=86)
Censored[a]	83 (50.9)	29 (33.7)
Time to deaths (KM) (months)[b]		
Median (95% CI)	41.1 (30.6, NE)	21.5 (17.4, 29.6)
Unstratified hazard ratio (T-VEC/GM-CSF)[c] **(95% CI)**	0.57 (0.40, 0.80)	
Unstratified log-rank test, p-value	0.0009	
Final OS data cut		
Subject status, n (%)		
Deaths	80 (49.1)	57 (66.3)
Censored[a]	83 (50.9)	29 (33.7)
Time to deaths (KM) (months)[b]		
Median (95% CI)	46.8 (31.2, NE)	21.5 (17.4, 29.6)
Unstratified hazard ratio (T-VEC/GM-CSF)[c] **(95% CI)**	0.56 (0.40, 0.79)	
Unstratified log-rank test, p-value	0.0008	

References: OPTiM[80]; Kaufman et al 2014[84]; Harrington et al 2015[82]

[a] Subjects that have not been recorded as dead are included as censored

[b] OS is calculated as the number of months from randomisation date to death date or last known to be alive date

[c] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio <1.0 indicates a lower average death rate and a longer overall survival for T-VEC relative to GM-CSF. 95% CI calculated from Cox regression model.

CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; KM, Kaplan-Meier; NE, non-estimable; OS, overall survival; T-VEC, talimogene laherparepvec

Over the course of the OPTiM study, the survival rate for patients with stage IIB-IVM1a disease was consistently higher in the T-VEC treatment group compared with the GM-CSF arm each year. After three years, the survival rate for patients in the T-VEC treatment group was 54.9% compared with a survival rate of 34.6% for patients in the GM-CSF treatment group. Moreover the survival rate in the T-VEC group appeared to be stable over 4 and 5 years, and 20% more T-VEC treated patients survived long term than those treated with GM-CSF (Table 4-15)[80].

Table 4-15: Kaplan-Meier OS rates by year in patients with stage IIIB-IVM1a disease – final OS data cut

Time	KM survival rate estimate, %		Treatment difference, % (95% CI)
	T-VEC (N=163)	GM-CSF (N=86)	
1-year	87.0	76.8	10.2 (-0.3, 20.7)
2-year	64.8	46.2	18.7 (5.6, 31.7)
3-year	54.9	34.6	20.3 (7.3, 33.2)
4-year	48.9	27.5	21.4 (8.2, 34.7)
5-year	48.9	NE[†]	-

Reference: Amgen data on file[80]

[†] The 5-year survival rate for the GM-CSF arm was not estimable because the last patient's follow up time ended before 60 months

CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; KM, Kaplan-Meier; NE, non-estimable; OS, overall survival; T-VEC, talimogene laherparepvec

Response Rates

Response rates (CR, PR and ORR) at the primary and final data cuts based on EAC assessment in patients with stage IIIB-IVM1a disease in the OPTiM study are shown in (Table 4-16).

The ORR (i.e. CR + PR) was higher in the T-VEC treatment group compared with the GM-CSF treatment group (40.5% [95% CI: 32.9, 48.4] versus 2.3% [95% CI: 0.3, 8.1] respectively; P<0.0001)[80].[80] Similarly, the proportions of patients with CR and PR were higher in the T-VEC treatment group compared with GM-CSF treatment group (16.6% versus 0% and 23.9% versus 2.3%, respectively)[80]. These findings were in line with results seen in the ITT population of the study (Appendix 1.4).

Table 4-16: Best overall response and ORR based on EAC assessment in patients with stage IIIB-IVM1a disease

	T-VEC (N=163)	GM-CSF (N=86)	Treatment difference (T-VEC/GM-CSF)
Primary data cut			
Response assessment based on EAC, n (%)			
CR	27 (16.6)	0 (0.0)	–
PR	39 (23.9)	2 (2.3)	–
Not in response	22 (13.5)	9 (10.5)	–
Not reviewed by EAC	75 (46.0)	75 (87.2)	–
ORR (CR + PR), n (%)	66 (40.5)	2 (2.3)	64 (38.2)
95% CI[a]	(32.9, 48.4)	(0.3, 8.1)	(28.2, 46.4)
p-value[b]	–	–	<0.0001
Final data cut			
Response assessment based on EAC, n (%)			
CR	27 (16.6)	0 (0.0)	–
PR	39 (23.9)	2 (2.3)	–
Not in response	22 (13.5)	9 (10.5)	–
Not reviewed by EAC	75 (46.0)	75 (87.2)	–
ORR (CR + PR), n (%)	66 (40.5)	2 (2.3)	64 (38.2)
95% CI[a]	(32.9, 48.4)	(0.3, 8.1)	(28.2, 46.4)
p-value[b]	–	–	<0.0001

References: Amgen data on file[80] _ENREF_83; Harrington et al 2015[82]

[a] The Clopper-Pearson method was used to calculate exact CIs for binary endpoints. Wilson's score method with continuity correction was used to calculate an approximate CI for between-group differences in binary rates

[b] Using Fisher's Exact Test

CI, confidence interval; CR, complete response; EAC, endpoint assessment committee; GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent-to-treat; ORR, objective response rate; PR, partial response; T-VEC, talimogene laherparepvec

Response onset

The time to response, in patients with stage IIIB-IVM1a disease, at the primary data cut was similar between the T-VEC (4.0 months) and GM-CSF treatment groups (3.8 months) (Table 4-17)[80].[80] This observation was consistent in the ITT population of the study (Appendix 1.4).

Table 4-17: Time to response per EAC in patients with stage IIIB-IVM1a disease

	T-VEC (N=163)	GM-CSF (N=86)
Primary data cut		
Time to response (months)[a]		
Median	4.0	3.8
95% CI	(3.2, 5.0)	(1.9, 5.6)
Final data cut		
Time to response (months)[a]		
Median	4.0	3.8
95% CI	(3.2, 5.0)	(1.9, 5.6)

Reference: Amgen data on file[80] ENREF 83

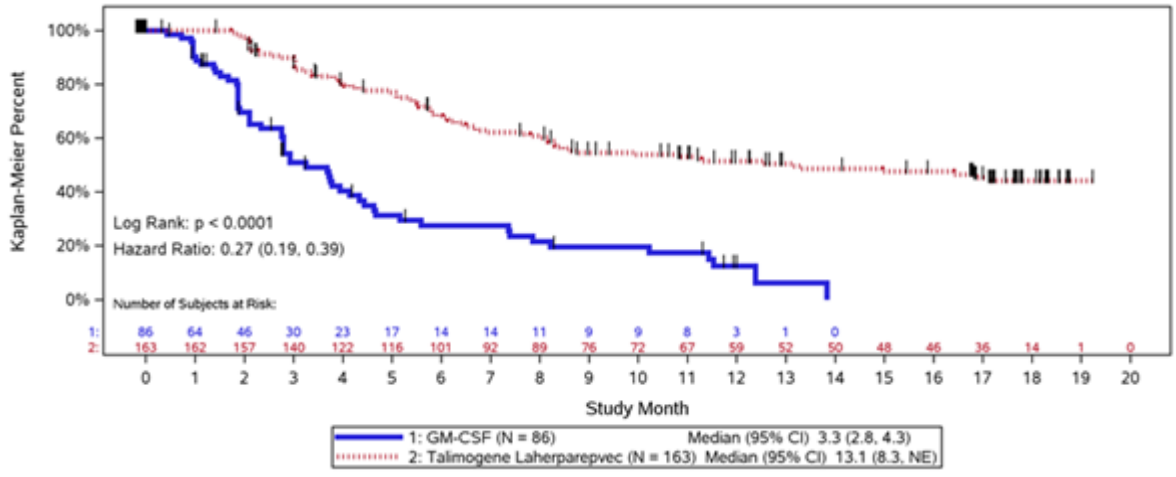
[a] The response onset is defined as the time from the date of randomization to the date of first documented evidence of response.

CI, confidence interval; EAC, endpoint assessment committee; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec

Time to Treatment Failure (TTF)

Analysis at the primary data cut revealed that the TTF per investigator assessment in patients with stage IIIB-IVM1a disease was greater in the T-VEC treatment group compared with the GM-CSF treatment group. Median TTF was 13.1 months for patients in the T-VEC treatment group compared with 3.3 months for patients in the GM-CSF treatment group (HR 0.27; 95% CI: 0.19, 0.39; P<0.0001) (Figure 4-7; Table 4-18)[80] ENREF 83. These findings were consistent with results seen in the ITT population of the study (Appendix 1.4).

Figure 4-7: Kaplan-Meier curves for TTF per investigator in patients with stage IIIB-IVM1a disease – primary data cut



Censor indicated by vertical bar |

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. Treatment failure is censored at the last tumour assessment if the patient has not yet experienced PDr or death.

Reference: Amgen data on file[80]

CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; NE, not estimable; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

Table 4-18: TTF per investigator assessment in patients with stage IIIB-IVM1a disease – primary 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, NE)	(2.8, 4.3)	–
Hazard ratio (T-VEC/GM-CSF)[b]	–	–	0.27
95% CI	–	–	(0.19, 0.39)
p-value	–	–	<0.0001

Reference: Amgen data on file[80] _ENREF_83

[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

Duration of response

As stated in Table 4-5, duration of response in the OPTiM study was defined as the longest individual period from the onset of a response (either PR or CR) to the first evaluable sign of the subject no longer meeting the response criteria or death (whichever event was earliest).

The duration of response for patients with stage IIIB-IVM1a disease during the OPTiM study was not estimable. This was consistent with the duration of response in the ITT population (see Appendix 1.4). However for those subjects who achieved CR, 88% (i.e. 9 out of 10) are still alive at 5 years.

Risk of Visceral and/or Bone Metastasis

Patients with stage IIIB-IVM1a melanoma are at high risk of developing visceral and/or bone metastasis. The effect of T-VEC versus GM-CSF on the risk to develop visceral/bone metastasis in patients with stage IIIB-IVM1a melanoma was evaluated using data from the OPTiM Study 05/005. Of 436 patients enrolled in the study, 249 patients had stage IIIB-IVM1a melanoma. Based on multivariate analysis, T-VEC patients with unresectable Stage IIIB-IVM1a melanoma had a 59% lower risk of developing visceral and bone metastases (hazard ratio [HR] = 0.41; p = 0.024) compared with GM-CSF patients. One-year visceral and/or bone metastasis-free survival was 81% in patients treated with T-VEC versus 53% in patients treated with GM-CSF[85].

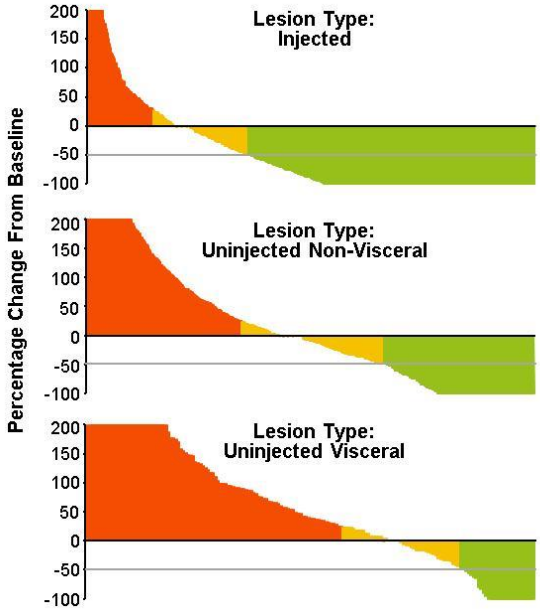
Evidence of Local and Systemic Effects of T-VEC Treatment

In the OPTiM study, exploratory analyses to evaluate the systemic activity of T-VEC (i.e. beyond local effects in injected lesions) found that responses were observed in non-injected

lesions, including non-visceral lesions (most commonly in the skin and lymph nodes) and visceral lesions (most commonly in the lung and liver). In analyses of patients with non-injected lesions, 27 of 79 patients (34.2%) had a ≥50% overall decrease in size in non-visceral lesions, and 8 of 71 patients (11.3%) had a ≥50% overall decrease in size in visceral lesions. Among 2,116 individual lesions directly injected with T-VEC, 1,361 (64.3%) decreased in size by ≥50% and 995 (47.0%) completely resolved. Of 981 non-injected non-visceral lesions, 331 (33.7%) decreased in size by ≥50% and 212 (21.6%) completely resolved. Of 177 visceral lesions, 27 (15.3%) decreased in size by ≥50%, the majority of which (16 [9.0%]) completely resolved (Figure 4-8)[86].

In patients with no visceral disease, among 1,441 individual lesions directly injected with T-VEC, 1026 (71.2%) decreased in size by ≥ 50% and 809 (56.1%) completely resolved. Of 538 non-injected lesions, 224 (41.6%) decreased in size by ≥ 50%, the majority of which (155 [28.8%]) completely resolved.

Figure 4-8: Responses to T-VEC at lesion-level and patient-level



Tumor area change: ≥ 25% > –50% to < 25% –100% to ≤ – 50%

Lesion (n = 2116)		Patient (n = 277)	
≥ 50% decrease	64%	OR	33%
100% decrease	47%	CR	15%

Lesion (n = 981)		Patient (n = 177)	
≥ 50% decrease	34%	OR	18%
100% decrease	22%	CR	6%

Lesion (n = 177)		Patient (n = 79)	
≥ 50% decrease	15%	OR	14%
100% decrease	9%	CR	3%

Note, subjects with evaluable lesions in the systemic effect analysis set. I.e. not based on Stage IIIB/C, IVM1a

Evaluable indicates at least 2 assessments with bi-dimensional measurements.

Injected lesion includes baseline or new lesion ever injected; Non-injected lesion includes baseline or new lesion never known to be injected

Abbreviations: CR, complete response; OR, overall response; T-VEC, talimogene laherparepvec.

Source: Andtbacka 2014[86]

4.8 Patient-Reported Outcomes and Health-related Quality of Life

Quality of life was assessed by the Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM) questionnaire in the OPTiM Study 005/05. The FACT-BRM has a total of 40 items that are categorised into 6 subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and 2 treatment-specific subscales (Additional Concerns-Physical and Additional Concerns-Mental). All 40 questions are combined to create an overall FACT-BRM score. Additional scores are the 6 subscales and the Trial Outcome Index (TOI) that is defined as the sum of the physical, functional, and treatment-specific subscales.

Table 4-19 reports the FACT-BRM completion rates over time in patients without visceral disease. In the GM-CSF arm, from very early on in the trial, a substantial percentage of patients did not complete the questionnaire. The difference in the completion rates between the two treatment arms is likely related to the difference between treatment arms in rates of treatment discontinuation, disease progression, and death.

Table 4-19: Completion rates for the FACT-BRM in patients with stage IIIB-IVM1a disease – primary data cut

	Completion rate, %	
Visit	**T-VEC (N=163)**	**GM-CSF (N=86)**
Cycle 1	95.7	82.6
Cycle 2	93.9	68.6
Cycle 3	89.6	53.5
Cycle 4	77.3	36.0
Cycle 5	69.9	26.7
Cycle 6	65.6	19.8
Cycle 7	60.7	16.3
Cycle 8	56.4	16.3

Reference: Amgen data on file[80]

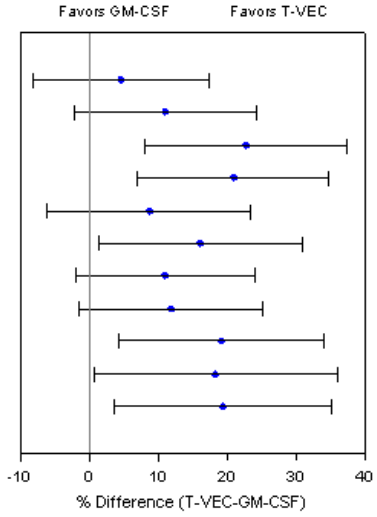
FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; GM-CSF, granulocyte–macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

Analyses were conducted in order to evaluate patient-level improvement in FACT-BRM TOI, total score, in the 6 subdomains, as well as in three individual items (overall quality of life [QoL], pain, and ability to work). Improvements in TOI were defined as increases of ≥ 5 points (range 0 to 108 points) from baseline that were sustained for ≥ 1 cycle (28 days starting at cycle 2). This measure of improvement is well-established as a clinically meaningful change within a group[87]. Improvements in individual domains were defined as increases of ≥ 2 points (range 0 to 50 points) from baseline that were sustained for ≥ 1 cycle. Improvements in individual items were defined as increases of ≥ 1 point (range 0 to 5 points) from baseline that were sustained for ≥ 1 cycle[87].

Compared to patients treated with GM-CSF, more patients treated with T-VEC had improvement in HRQoL assessed by all of these 11 measures based on FACT-BRM. The differences in 6 of 11 measures reached statistical significance, including Emotional Well-Being, Functional Well-Being, Social/Family Well-Being, overall QoL, pain, and ability to work (Figure 4-9).

Figure 4-9: Improvement Rates of Patient Report Outcome by Treatment of T-VEC and GM-CSF Stage IIIB/C, IVM1a ITT Subjects Evaluable for Domain Improvement

Subscale	N	Rate GM-CSF	Rate T-VEC	% Difference (95% CI)
Trial Outcome Index	207	23.4%	28.0%	4.5% (-8.2% - 17.3%)
FACT-BRM Total	215	26.9%	37.8%	11.0% (-2.2% - 24.2%)
Emotional Well-Being	197	31.6%	54.3%	22.7% (8.1% - 37.3%)
Functional Well-Being	193	25.8%	46.6%	20.8% (6.9% - 34.6%)
Physical Well-Being	130	18.2%	26.7%	8.6% (-6.2% - 23.3%)
Social/Family Well-Being	152	21.6%	37.6%	16.1% (1.3% - 30.8%)
Additional Concerns: Physical	186	20.0%	31.0%	11.0% (-2.0% - 23.9%)
Additional Concerns: Mental	189	22.0%	33.8%	11.8% (-1.5% - 25.2%)
QoL	157	22.4%	41.7%	19.2% (4.3% - 34.1%)
Pain	106	20.6%	38.9%	18.3% (0.7% - 36.0%)
Ability to Work	134	20.0%	39.4%	19.4% (3.5% - 35.2%)



Scores from unscheduled visits were not included
A subject is considered evaluable for a domain if baseline score is not the best score and has at least one post-baseline score
TOI and total improvements are defined as >=5-point score increase from baseline with a >=1 cycle duration
QoL, pain and work improvements are defined as >=1-point score increase from baseline with a >=1 cycle duration
Other improvements are defined as >=2-point score increase from baseline with a >=1 cycle duration
Abbreviations: CI, confidence interval; GM-CSF, granulocyte–macrophage colony-stimulating factor; ITT, intent-to-treat; QoL, overall quality of life; T-VEC, talimogene laherparepvec.
Source:Amgen data on file[80]

4.9 Subgroup analysis

Not applicable.

4.10 Meta-analysis

A meta-analysis of T-VEC trials only was not conducted as there was only one randomised controlled trial for T-VEC (i.e. the OPTiM study). Furthermore, as described previously the comparator in this trial, GM-CSF, is not a relevant comparator as defined in the decision problem.

4.11 Indirect and mixed treatment comparisons

Network meta-analysis feasibility assessment

As previously described in Section 4.1, the relevant clinical evidence for T-VEC comes from the OPTiM trial[79] evaluating efficacy of T-VEC versus GM-CSF. There were no head-to-head RCTs comparing T-VEC with the relevant comparators defined in the decision problem. In

order to address the decision problem set out in the appraisal, efforts were made to conduct a NMA to evaluate T-VEC versus relevant comparators.

Search strategy and study selection

A total of 59 studies were identified in the SLR (methods and results reported in Section 4.1). However from examination of this evidence base, it was clear that T-VEC had not been evaluated against any comparator other than granulocyte-macrophage colony-stimulating factor (GM-CSF) in the OPTiM trial, and similarly that GM-CSF had not been evaluated in any other comparator trials. Therefore the OPTiM trial was isolated, with no common comparator with other published trials or publically available data and could not be linked to an evidence network with any comparators, thus making a traditional NMA unfeasible.

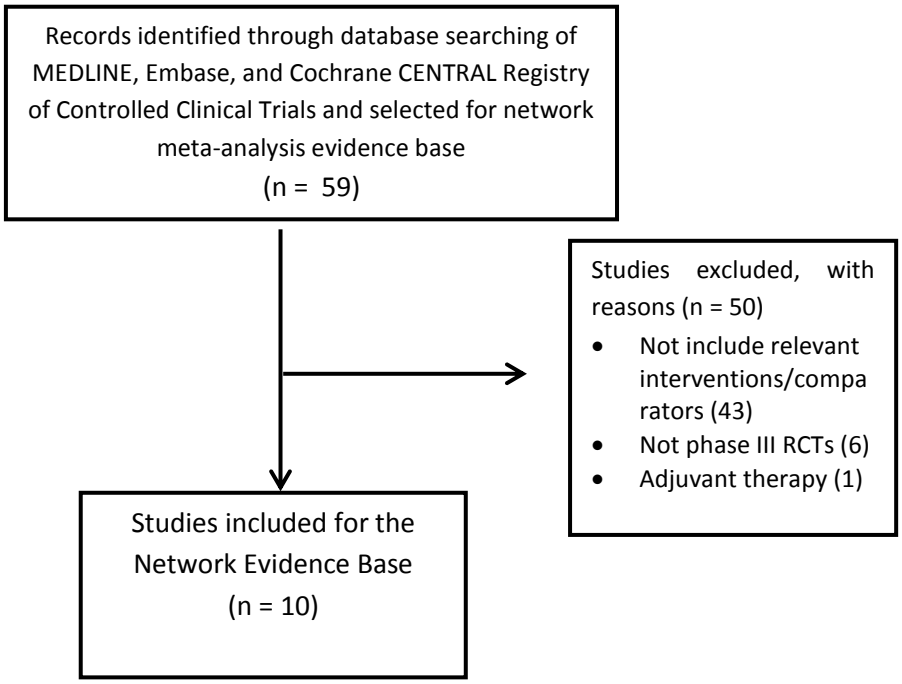
In order to present and describe the key evidence relevant to the decision problem; a simple (broken) network was constructed by selecting only phase III RCTs which evaluated the relevant intervention/comparators as a monotherapy (as defined in the NICE scope), for the treatment of patients with stage IIIB-IV melanoma. Criteria for study inclusion/exclusion to define the NMA evidence base for this (broken) network are described in Table 4-20. Details of study inclusion and exclusion are presented in the PRISMA flow diagram in Figure 4-10.

Table 4-20: Criteria used in selection of the NMA evidence base

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Studies in adults with stage IIIB-IV melanoma, as defined in the decision problem	Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma. Did not report on the population of interest
Intervention/comparators	Studies with least one treatment arm evaluating the relevant intervention or comparator as defined in the decision problem (T-VEC, ipilimumab, vemurafenib or dabrafenib) as a monotherapy.	Studies did not include one treatment arm with relevant interventions/comparators
Outcomes	Studies reporting at least one of the following outcomes: OS PFS	Studies did not report outcomes of interest
Trial design	Phase III RCTs	Not Phase III RCTs

NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; T-VEC, talimogene laherparepvec

Figure 4-10: PRISMA flow diagram showing study inclusion/exclusion for the NMA evidence base



NMA, network meta-analysis; RCT, randomised controlled trial

A total of 10 studies were included in the NMA evidence base, as listed in Table 4-21. The network is shown diagrammatically in (Figure 4-11).

Table 4-21: List of studies included in the NMA evidence base

	References of trial	Trial design	Trial drugs (n per arm)	Dabrafenib	GM-CSF	Ipilimumab	T-VEC	Vemurafenib
1.	CA184-024 Robert 2011; Maio 2015	Phase III, DB RCT	IPI + DTIC (n=250) DTIC (n=252)	--	--	yes	--	--
2.	BRIM-3 Chapman 2011; McArthur 2014	Phase III RCT	VEM (n=337) DTIC (n=338)	--	--	--	--	yes
3.	CheckMate 067 Larkin 2015	Phase III, DB RCT	NIV 3 mg/kg (n=316) NIV 1 mg/kg + IPI 3 mg/kg (n=314) IPI 3 mg/kg (n=315)	--	--	yes	--	--
4.	MDX010-20 Hodi 2010; Weber 2013; McDermott 2013; Harvey 2013	Phase III, DB RCT	IPI + gp100 (n=403) IPI (n=137) gp100 (n=136)	--	--	yes	--	--
5.	KEYNOTE-006 Robert 2015	Phase III RCT	PEM 10 mg/kg (n=279) PEM 3 mg/kg (n=277) IPI 3 mg/kg (n=278)	--	--	yes	--	--
6.	COMBI-V Robert 2015	Phase III, OL RCT	Dabrafenib + trametinib (n=352) VEM (n=241)	--	--	--	--	yes
7.	COMBI-D Long 2014	Phase III, DB RCT	Dabrafenib + trametinib (n=211) Dabrafenib (n=212)	yes	--	--	--	--
8.	BREAK-3 Hauschild 2012; 2013 2014	Phase III, OL RCT	Dabrafenib (n=187) DTIC (n=63)	yes	--	--	--	--

	References of trial	Trial design	Trial drugs (n per arm)	Dabrafenib	GM-CSF	Ipilimumab	T-VEC	Vemurafenib
9.	coBRIM Larkin 2014	Phase III RCT	VEM + cobimetinib (n=248) VEM (n=247)	--	--	--	--	yes
10.	OPTiM Andtbacka 2014	RCT phase III	T-VEC (n=295) GM-CSF (n=141)		yes		yes	

Methods and results of included studies

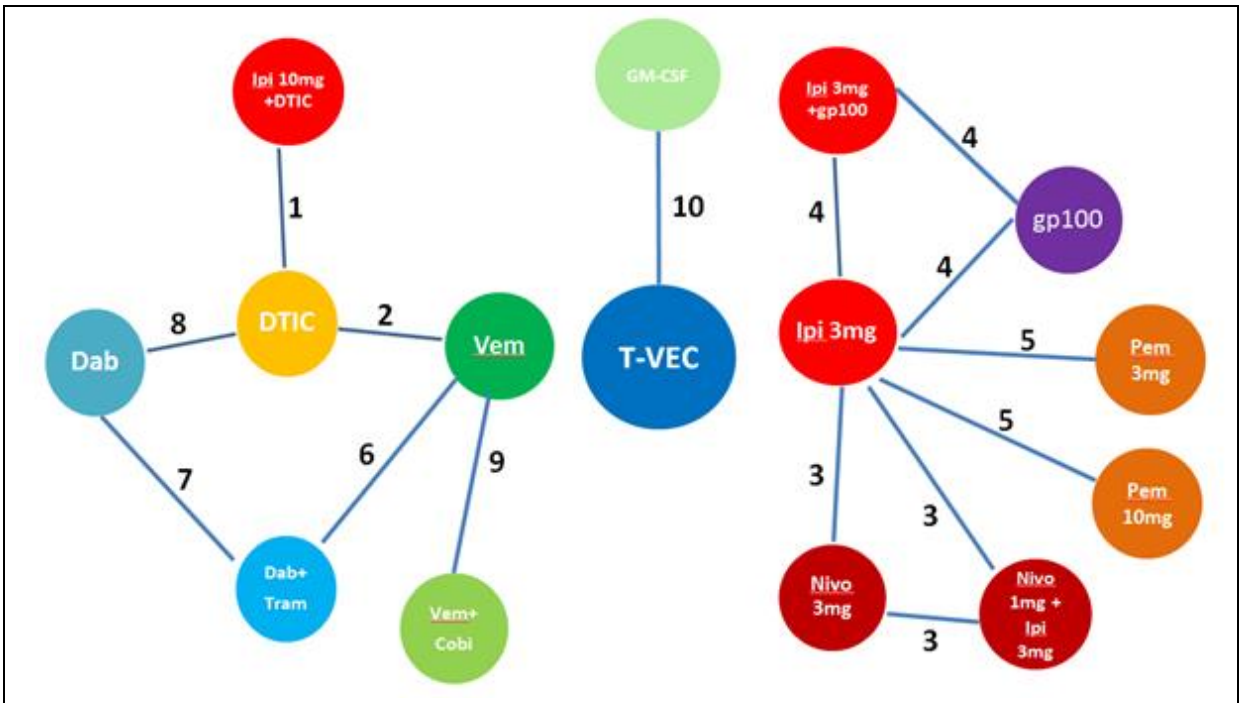
A summary of methods, outcomes, results and baseline characteristics of the included studies (excluding OPTiM) are presented in Appendix 1.4.

All 10 RCTs reported appropriate efficacy results for the broad population of patients with stage III-IV metastatic melanoma. However for the proposed licensed indication for T-VEC in non-visceral metastatic disease (stage IIIB-IVM1a), only the OPTiM trial had a high proportion of patients with non-visceral disease, with 57%, compared with RCTs for ipilimumab (11%-17%), vemurafenib (18%-23%) and dabrafenib (16% and 20%), where most patients had later stage metastatic disease (stage IVM1b-IVM1c). The pivotal trial for T-VEC therefore included an exploratory analysis of patients with stage IIIB-IVM1a metastatic disease (which formed the basis for the proposed licensed indication for T-VEC in non-visceral metastatic disease). However for comparator RCTs, there was minimal reporting of subgroup analyses for these patients in the published literature.

Assessment of risk of bias for each of the studies included in NMA evidence base is presented in Appendix 1.4. Overall, the selected studies had a low risk of bias. In general, randomisation was carried out appropriately, groups were similar at baseline and there were no unexpected imbalances in the number of drop-outs between groups. There was low risk of selective reporting bias and most studies conducted an intention-to-treat analysis.

A network diagram for the 10 studies identified, showing the broken network, is presented in Figure 4-11.

Figure 4-11: Network diagram for studies of therapies for metastatic melanoma



Numbers correspond to the study numbers in

Table 4-21
References: Robert et al 2011[88]; Maio et al 2015[89]; Chapman et al 2011[71]; McArthur et al 2014[90] Larkin et al 2015[91]; Hodi et al 2010[72]; Weber et al 2013[92]; McDermott et al 2013[93]; Harvey et al 2013; Robert et al 2015 (KEYNOTE-006)[95]; Robert et al 2015 (COMBI-V)[96]; Long et al 2014[97]; Hauschild et al 2012[98]; Hauschild et al 2013[99] Hauschild et al 2014[100]; Larkin et al 2014[101]; Andtbacka et al 2014[102]

Cobi, cobimetinib; Dab, dabrafenib; DTIC, dacarbazine; GM-CSF, granulocyte macrophage colony-stimulating factor; gp100, glycoprotein 100; Nivo, nivolumab; Ipi, ipilimumab; Pem, pembrolizumab; Tram, trametinib; T-VEC, talimogene laherparepvec; Vem, vemurafenib

In addition to the broken network, the clinical similarity of studies within the network was assessed by evaluating differences in potential treatment effect modifiers within the study and patient characteristics (e.g. stage of disease, LDH levels and ECOG performance status). Stage of disease is a known treatment effect modifier[22]; with earlier stage metastatic disease (stage III) associated with lower risk of mortality than later stage metastatic disease (stage IV). The substantial differences between the patient population enrolled in the OPTiM trial (in which 57% of patients had stage IIIB-IVM1a disease) compared with the comparator RCTs (in which only 11-23% of patients had stage IIIB-IVM1a disease)[79], meant that the RCTs within the network were heterogeneous and therefore not comparable even if there were a connected network. Given the challenges of both a disconnected network and in such different populations, it was concluded that a NMA was not feasible.

Assessment of alternative methods for comparative effectiveness

Evaluation of alternative methods

The pivotal trial for T-VEC included an exploratory analysis of patients with stage IIIB- IVM1a metastatic disease (which formed the basis for the proposed licensed indication for T-VEC in non-visceral metastatic disease); this subgroup comprised more than 50% of the trial population in contrast to comparator trials which included less than 20% of patients with stage IIIB-IVM1a metastatic disease. Furthermore, for comparator RCTs, there was minimal reporting of subgroup analyses for these patients in the published literature. In addition, individual patient data is only available for the T-VEC trial, which presents a further challenge for potential alternative methods that could be utilised to determine the comparative efficacy of T-VEC versus the relevant comparators. In order to overcome the challenges relating to a disconnected network of evidence and the differences in trial patient characteristics between T-VEC and the relevant comparators in this appraisal, five alternative indirect comparison methods were considered and their feasibility assessed.

1. Matching-adjusted indirect comparison (MAIC)
   MAIC uses individual patient-level data (IPD) from trials of treatment A to match baseline summary statistics reported from trials of treatment B. After matching, using an approach similar to propensity score weighting, survival outcome for treatment A can be adjusted according to the patient characteristics of treatment B, so that the adjusted survival outcome of treatment A reflects the survival if treatment A had treated treatment B's patient population (Caro et al. 2010; Ishak et al. 2015).

2. Simulated treatment comparison (STC)
   STCs is conceptually similar to MAIC, in that it uses patient-level data on treatment A (index trial) and published summary data on treatment B (comparators). STC creates a predictive equation for the survival outcome using patient-level data on treatment A. This

equation is used to predict the survival that would have been observed for treatment A in patients with characteristics of treatment B (Signorovitch et al. 2010).

3. American Joint Committee on Cancer (AJCC) adjustment
   This adjustment uses published, long-term survival data by stage for melanoma from the AJCC as the common reference to adjust survival outcomes based on disease stage distribution from each trial.

4. Korn prediction model
   Korn et al developed a model to predict OS using pooled data from 2100 patients from 42 trials conducted between 1975 and 2005 with a variety of regimens in metastatic melanoma[103]. The Korn model was based on four prognostic factors: gender, ECOG performance status, presence of visceral metastases, and presence of brain metastases. The Korn prediction model can be used to adjust the OS and PFS data from each comparator trial based upon the patient characteristics in the OPTiM trial, so that the adjusted comparator OS and PFS curve for the comparator would represent the expected survival if the patients in the comparator trial had a similar distribution of patient characteristics as those in the OPTiM trial.

   The Korn prediction model can also be utilised through the model-based meta-analysis (MBMA) method which uses a multivariable hierarchical survival model developed using the Korn algorithm as a reference. The regression-based model estimates treatment effect for each comparator controlling for baseline patient characteristics (gender, ECOG performance status, visceral status, brain metastases, and LDH status). This model uses counterfactual simulation to generate an adjusted OS curve for each comparator by applying T-VEC trial patient characteristics and the comparator treatment effect.

5. Modified Korn prediction model
   In 2014, the manufacturer of ipilimumab in their NICE submission for previously untreated metastatic malignant melanoma, modified the original Korn model to include the presence of elevated LDH levels as a fifth factor. The modified Korn prediction model can then be used to adjust the OS and PFS data from each comparator trial using a similar approach previously outlined for the original Korn prediction model.

The feasibility of both the MAIC and STC methods depends on the compatibility of patient populations studied in the T-VEC trial and comparator trials. Given that substantial differences exist in patient populations included in the T-VEC and comparator trials, and given that individual patient level data is only available for T-VEC, the MAIC and STC methods can be used to adjust the T-VEC outcomes to the comparator population (i.e. visceral metastatic disease). The relative effects derived from the STC or MAIC could be applied to the T-VEC outcomes to generate estimates of efficacy in the stage IIIB-IVM1a population. However, treatment effect may differ according to the presence of visceral disease and also by treatment, which is the case for T-VEC, and therefore these methods do not capture potentially important treatment interactions across subgroups.

The alternative approaches to adjustment using previously published prognostic equations such as the AJCC and the Korn prediction equation could be considered as viable alternatives in this context. It is noteworthy that the AJCC adjustment only adjusts for one

variable, differences in disease stage across trials, and does not adjust for any other variable including other key patient prognostic characteristics. This is likely to result in a very limited adjustment for the comparators. The Korn prediction model offers a viable alternative. However, given that it includes four prognostic variables, it appears less appropriate than modified Korn prediction model which includes a fifth important prognostic variable, high LDH. It is also noteworthy that the MBMA method that utilises the Korn prediction equation has similar limitations to the MAIC and STC approaches, in that it ignores interactions between covariates and hence will not yield appropriate estimates of treatment effectis in the subgroup with no visceral disease.

Recommendation

There is no single gold standard approach to dealing with the problem of comparing treatments between disconnected networks, and consequently the methodology chosen would depend on the context as well as the availability of data. In the presence of important treatment- subgroup interactions reported for TVEC, the modified Korn prediction model appears to present the most appropriate approach. This approach includes key patient prognostic characteristics and also takes into account additional risk factors associated with short survival such as high LDH[104]. It includes the covariate, presence of visceral disease, and thereby captures the impact of non-visceral metastatic disease versus visceral metastatic disease on survival. Importantly, the modified Korn methodology has also been used and accepted in a previous NICE appraisal (TA319)[2] evaluating melanoma and this precedent further supports the case for using this approach in the current context.

The modified Korn model was used in this submission to compare survival outcomes for T-VEC and the primary clinical comparator ipilimumab, after adjusting for prognostic differences between the characteristics of the populations of the OPTiM and the ipilimumab trials. It is noteworthy that the meta-analysis on which the Korn algorithm was estimated is for all patients and is not dependent on $BRAF_{V600}$ status, which is a critical prognostic gene for the BRAF inhibitors vemurafenib and dabrafenib. This is likely to render the adjusted overall survival for the BRAF inhibitors uncertain. Indeed, this issue with respect to the application of the Korn model to the BRAF inhibitors was highlighted in the recent pembrolizumab submission to NICE and the Evidence Review Group similarly deemed this analysis and results as unreliable.

Given the absence of data for ipilimumab in patients with non-visceral metastatic disease it is highly uncertain whether there would also be a treatment-subgroup interaction effect for ipilimumab in this group of patients. The modified Korn captures the prognostic differences between the overall trial population and the subgroup with non-visceral metastatic disease but assumes the absence of potential treatment-subgroup interactions between treatment effect in the overall trial population and the subgroup of patients with non-visceral metastatic disease. The assumption of a potential interaction effect for ipilimumab was therefore considered using a two-step Korn adjustment. The two-step Korn adjustment uses the same modified Korn equation to account for prognostic differences (1st-step) but includes an additional adjustment to capture a possible treatment-subgroup interaction effect between ipilimumab and stage of disease (2nd step). However, it is important to note that while the 2nd step allows for a potential treatment-subgroup interaction effect for ipilimumab, both the

existence and possible magnitude of such an effect appears highly uncertain based on existing evidence.

Therefore two approaches with respect to the Korn adjustment were considered: (i) the modified Korn method which includes a key fifth prognostic factor LDH, but assumes the absence of a treatment-subgroup interaction effect for ipilimumab in the T-VEC licensed population, and (ii) the two-step Korn adjustment which includes an additional potential interaction effect for ipilimumab in the non-visceral metastatic population.

Search methodology and studies identified for inclusion in the modified Korn analysis

The search methodology and studies identified for inclusion in the modified Korn analysis are discussed below.

The evidence used in the application of the Korn methodology included those RCTs which evaluated T-VEC and ipilimumab and reported OS data, and used the pivotal RCT for T-VEC (OPTiM) and the two pivotal RCTs for ipilimumab (MDX010-20 and CA184-024).

Search strategy and study selection

Only a subgroup of the 10 RCTs identified for the NMA feasibility assessment were relevant for use in the application of the Korn methodology, specifically; those phase III RCTs which evaluated T-VEC and the primary clinical comparator, ipilimumab, and reported OS. Details of inclusion/exclusion criteria to define the evidence are presented in Appendix 1.4.

A total of three trials were identified to form the evidence base for the modified Korn analysis and are summarised in Table 4-22. A list of further studies excluded and the reasons why are presented in the Appendix 1.4.

Table 4-22: List of studies included in the evidence base for the modified Korn model

	Trial name/ID	Intervention	Primary Reference	Notes
1	OPTiM 005/05	T-VEC vs GM-CSF	Kaufman 2014[84]	
2	MDX010-20	IPI monotherapy vs IPI in combination with gp100 and gp100	Hodi 2010[72]	
3	CA184-024	IPI + DTIC vs DTIC monotherapy	BMS NICE submission 2014[2]; Robert 2011[88]	

BMS, Bristol Myers Squibb; DTIC, dacarbazine; GM-CSF, granulocyte macrophase-colony stimulating factor; IPI, ipilimumab; T-VEC talimongene laherparepvec

Methods and outcomes of included studies;

A summary of methods, outcomes, results and baseline characteristics of the included studies are presented in Appendix X. Overall, the selected studies had a low risk of bias. In general, randomisation was carried out appropriately, groups were similar at baseline and there were no unexpected imbalances in the number of drop-outs between groups. There was low risk of selective reporting bias and most studies conducted an intention-to-treat

analysis. Assessment of risk of bias for each of the studies included in the meta-analysis is presented in Appendix 1.4.

Comparison of baseline patient characteristics of included studies

The baseline characteristics of the participants in the pivotal trials for T-VEC and ipilimumab are not comparable across the different RCTs. It is noteworthy that the ITT population in the OPTiM study included 57% of patients in earlier stage as defined by metastases stage IIIB, IIIC and IVM1a compared to 11%-23% of patients in the comparator trials.

A detailed comparison of the baseline patient characteristics of the licensed population of T-VEC and the comparator populations is presented in Table 4-23. Although the baseline characteristics were generally similar across the trials for age and gender, there were differences in the ECOG performance status, LDH levels, and the stage of metastases. The MDX010-20 trial of ipilimumab use in second-line had just over 50% with ECOG status of 0 compared to TVEC trial population (as per license) of 74%. Further, the ipilimumab trials included a higher proportion of patients with LDH levels > ULN ranging from between 37% to 39% compared to 1% for T-VEC. Importantly, the T-VEC licensed population all had earlier stage metastatic disease and consequently no visceral metastases which is in contrast to the comparator trials whose populations included patients with later stage metastatic disease, i.e. less than one-fifth of patients without any visceral metastases.

Table 4-23: Comparison of patient baseline characteristics from OPTiM and ipilimumab trials MDX010-20 and CA184-024

Patient characteristic	**OPTiM ITT[79] (T-VEC, N=295)**	**OPTiM Patients with stage IIIB-IVM1a disease[82] (T-VEC, N=163)**	**MDX010-20[72] (Ipi, N=137)**	**CA184-024[2,88] (Ipi, N = 250)**
Age	Median: 63.1	Median: 63.0	Mean:56.8	Mean:57.5
Gender (%)				
Male	59	56	59	61
Female	41	44	41	39
ECOG status (%)				
0	71	74	53	71
>=1	28	26	47	29
Unknown	1	1	0	0
No visceral disease (%)*	55	100	11	17
Stage (%)[†]				
IIIB	8	14	1	2
IIIC	22	41		
IVM1a	25	46	10	15
IVM1b	22	-	16	26
IVM1c	23	-	73	57

Patient characteristic	OPTiM ITT[79] (T-VEC, N=295)	OPTiM Patients with stage IIIB-IVM1a disease[82] (T-VEC, N=163)	MDX010-20[72] (Ipi, N=137)	CA184-024[2,88] (Ipi, N = 250)
Unknown	<1	0		
Brain metastases (%)				
No	99	100	89	99
Yes	1	,0	11	1
LDH (%)				
≤ULN	90	95	61	63
>ULN	5	1	39	37
Unknown	5	4	0	0

*Visceral disease defined as inclusion of stage IIIB-IVM1a and exclusion of stage IVM1b-IVM1c
† note values are rounded up to the nearest whole number
- = value not available
ECOG, Eastern cooperative oncology group; Ipi, ipilimumab; ITT, intent to treat; LDH, Lactate dehydrogenese; T-VEC, talimogene laherparepvec ULN, upper limit of normal

The modified Korn prediction model

Development

The model reported by Korn et al (2008)[103] allows the prediction of overall survival for metastatic melanoma patients based on four prognostic characteristics: Gender, ECOG performance status, tumour stage and presence of brain metastases. Korn et al. developed prediction models using individual patient-level data from 42 phase 2 studies, in 2100 patients with metastatic melanoma, conducted between 1975 and 2005.

Korn reported the coefficients for these four prognostic factors on relative risk. The equation with the estimated parameters for the four prognostic covariates was defined as follows:

$$\log(\widehat{HR}) = 0.248X_{Gender=Male} + 0.436X_{ECOG=1} + 0.948X_{ECOG\geq 2} \mp 0.421X_{Visceral=YES} + 0.304X_{Brain=YES}$$

The manufacturer of ipilimumab, BMS, in their most recent NICE single technology appraisal submission for previously untreated metastatic malignant melanoma, modified the original Korn model by including the presence of elevated serum lactate dehydrogenase level (LDH) levels as a fifth prognostic variable. An elevated LDH level is a powerful adverse predictor of survival and has been reported to be an important independent prognostic factor in metastatic melanoma[104]. Furthermore, the correlation between increased LDH and decreased survival among patients with advanced melanoma has been confirmed by numerous studies investigating various prognostic factors[105-113].

The modified Korn equation with the estimated parameters for the five prognostic covariates was defined as follows:

$$\log(\widehat{HR}) = -0.154X_{Gender=Female} - 0.400X_{ECOG=0} - 0.285X_{Visceral=NO} - 0.306X_{Brain=NO} - 0.782X_{LDH=Normal}$$

The Korn et al. (2008)[103] prediction model has been used in unresectable stage III/IV melanoma disease to allow comparisons to be made between treatments in studies with no common comparator and in which there were differences between studies in prognostic factors. This approach has been used in recent submissions to NICE to allow comparisons to be made between treatments in studies with no common comparator and in which there were differences between studies in prognostic factors, ipilimumab for previously untreated advanced malignant melanoma and pembrolizumab for previously untreated advanced malignant melanoma patients. It has also been used by Kotapati et al., (2011)[114] to estimate overall survival of ipilimumab in the management of pre-treated patients with unresectable stage III/IV melanoma.

Modified Korn-adjusted method to predict survival outcomes for T-VEC versus its comparators

The implementation of the modified Korn adjustment and the consequent results of the adjusted OS and PFS are presented in this section. In the absence of a Korn equation for PFS and the high correlation likely between PFS and OS, the same adjustments were to PFS as applied.

The following steps were implemented to calculate the adjusted survival (OS and PFS) for the ipilimumab had they treated a population similar to that of the T-VEC licensed population.

Methods

1. The modified Korn model was used to adjust the Kaplan Meier data for differences between the patient and disease characteristics at baseline using the following five baseline prognostic factors:
   - Gender (female vs. male)
   - ECOG performance status (0 vs. >0)
   - Presence of visceral metastases (No vs. Yes)
   - Presence of brain metastases (No vs. Yes)
   - LDH (Normal vs. Elevated)

2. The adjustment factor to adjust the comparator trial to match T-VEC patient characteristics was estimated.
   First, hazard ratios that account for the distributional differences in these five factors were estimated. Each comparator trial's baseline distribution values was substituted into the log(HR) equation for the five baseline prognostic factors taken from modified Korn model (NICE TA319):

$$\log(\widehat{HR}) = -0.154X_{Gender=Female} - 0.400X_{ECOG=0} - 0.285X_{Visceral=NO} - 0.306X_{Brain=NO} - 0.782X_{LDH=Normal}$$

The same was done for the T-VEC licensed population in the OPTiM study. The difference in log(HR)s for the T-VEC licensed population and comparator trials ITT population reflect the size of the difference in outcomes due to differences in patient populations. Specifically this reflects the differences in the prognosis of patients between the licensed population in the T-VEC study, who were all stage IIIA-IVM1a patients with no visceral metastases, and the comparator trials which had a majority of patients with later stage metastatic disease and consequently a worse prognosis.

An adjustment factor was calculated from the hazard ratios such that:

$$HR\left(\frac{TVEC_{baseline\ characteristics}}{COMPARATOR_{baseline\ characteristics}}\right) = \frac{HR_{TVEC_{baseline\ characteristics}}}{HR_{Comparator_{baseline\ characteristics}}}$$

The calculated HRs and adjustment factors are presented in Table 4-24. The adjustment factors adjust the worse prognosis of patients in the comparator trials to the baseline characteristics patients had in the T-VEC licensed population (non-visceral metastatic disease) in the OPTiM trial. The lower the adjustment factor, the bigger the upward adjustment in survival for ipilimumab.

Table 4-24: Model Coefficients and Adjustment Factors for OS and PFS

Treatment	HR equations	Hazard Ratios	Adjustment Factor
T-VEC stage IIIB-IVM1a	$\log(\widehat{HR}) = -0.154X_{Gender=0.44} - 0.400X_{ECOG=0.74} - 0.285X_{Visceral=1} - 0.306X_{Brain=1} - 0.782X_{LDH=0.94}$	0.18	NA
Ipilimumab ITT (previously untreated)*	$\log(\widehat{HR}) = -0.154X_{Gender=0.39} - 0.400X_{ECOG=0.71} - 0.285X_{Visceral=1} - 0.306X_{Brain=0.99} - 0.782X_{LDH=0.63}$	0.31	0.60
Ipilimumab ITT (previously treated)	$\log(\widehat{HR}) = -0.154X_{Gender=0.41} - 0.400X_{ECOG=0.53} - 0.285X_{Visceral=0.11} - 0.306X_{Brain=0.89} - 0.782X_{LDH=0.61}$	0.35	0.53
*In the BMS NICE submission for ipilimumab in previously untreated patients, an OS was derived for monotherapy ipilimumab at 3mg/kg for the previously untreated study population. The adjustment factor calculated in this analysis was applied to the derived OS data HR, hazard ratio; ITT, intent to treat; OS, overall survival; PFS, progression free survival; T-VEC, talimongene laherparepvec			

3. The adjusted survival (OS and PFS) for each comparator was estimated by adjusting the Kaplan Meier curves from each comparator using the calculated adjustment factor to reflect outcomes in an T-VEC-like population:

$$S(t)_{NEW} = S(t)_{OLD}^{HR\left(\frac{TVEC}{TRIAL}\right)}$$

4. The uncertainty surrounding the adjustment of OS was characterised by a 95% prediction interval. The standard errors provided in TA319 for the modified Korn equation was used to generate the 95% CI for the HR.

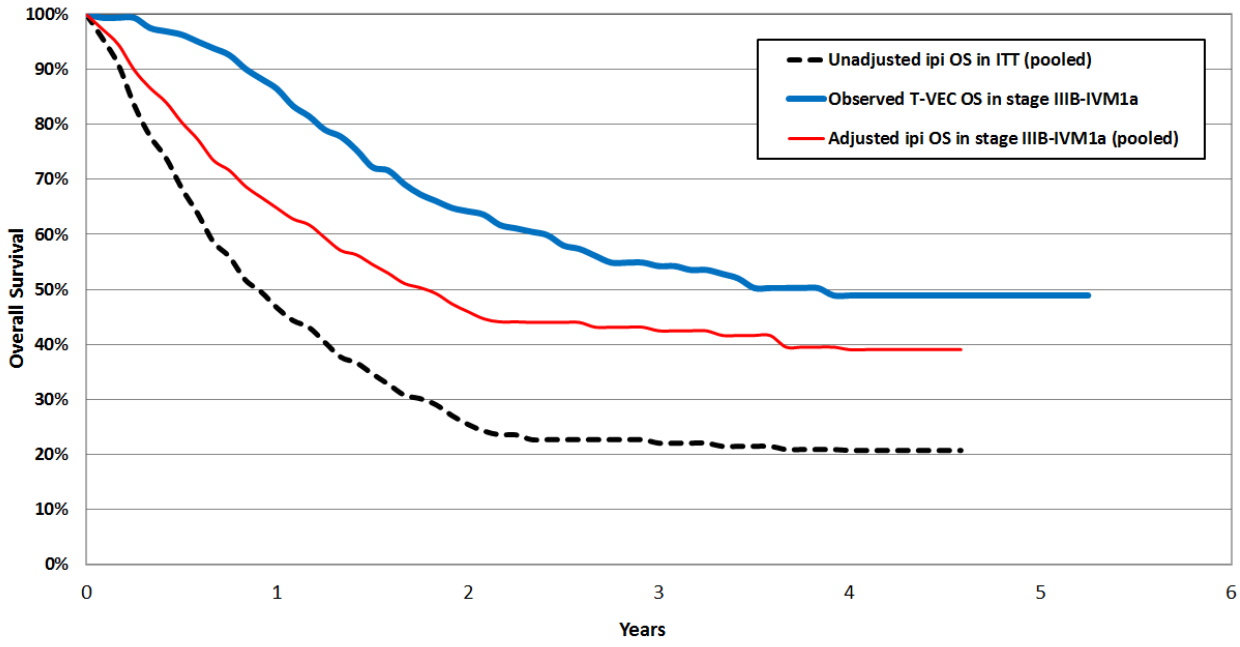
5. In case multiple curves are available for the same comparator, they are pooled by the modified Mantel-Haenszel method.

Results - median overall survival and Progression-free survival

The median OS and PFS results from the meta-analysis using the modified Korn adjustment are shown in Figure 4-12 and Figure 4-13. The adjustment factor serves to adjust upwards the original Kaplan Meier curves such that they reflect the survival that would have been observed had ipilimumab treated a T-VEC licensed population. In the case of ipilimumab, the application of the modified Korn adjustment to adjust the ipilimumab patient population to reflect that of the licensed population for T-VEC doubles the median OS for ipilimumab (pooled) from 10.8 months to 21.3 months.

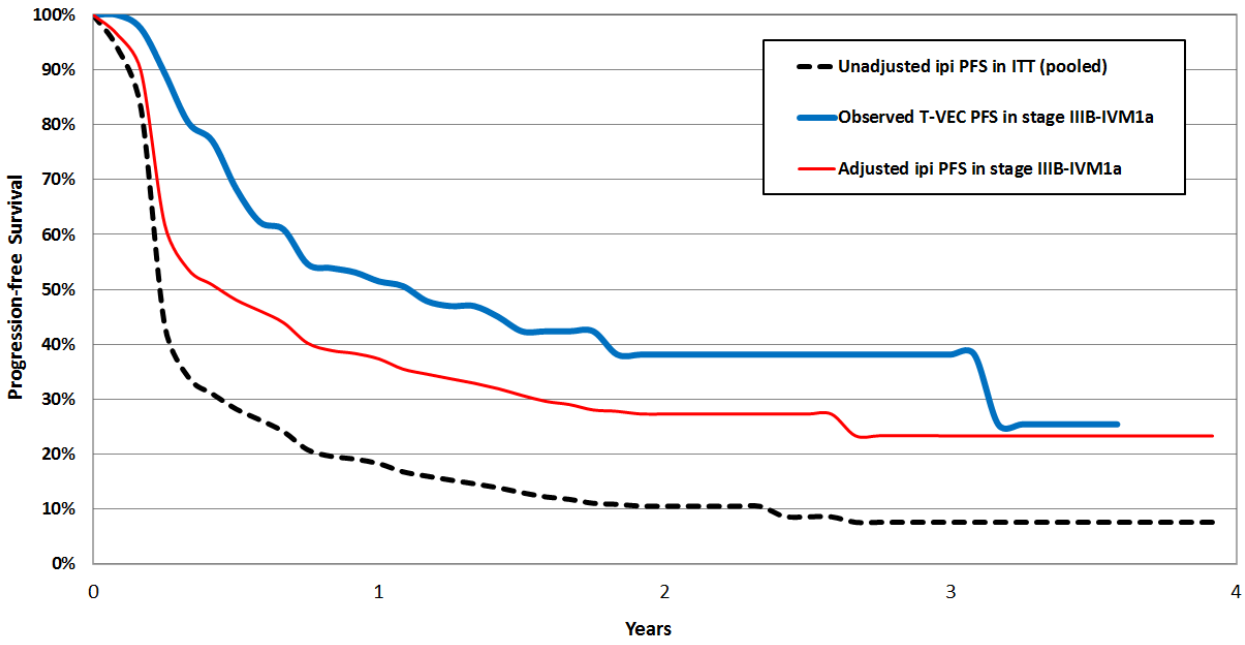
Figure 4-14 illustrates the uncertainty surrounding the adjustment with ipilimumab as characterised by the 95% prediction interval.

Figure 4-12: Modified Korn adjusted OS curve for ipilimumab in patients with stage IIIB-IVM1a disease



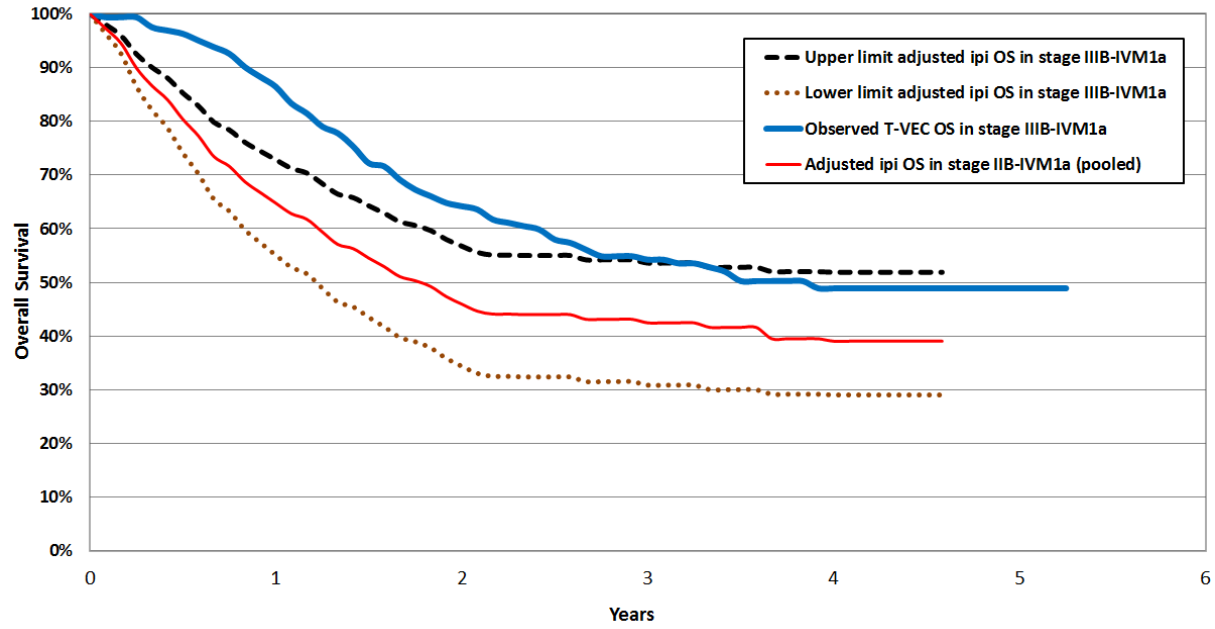
Abbreviations: OS, overall survival; ipi, ipilimumab; T-VEC, talimogene laherparepvec

Figure 4-13: Modified Korn adjusted PFS curve for ipilimumab in patients with stage IIIB-IVM1a disease



Abbreviations: ipi, ipilimumab; PFS, progression free survival; T-VEC, talimogene laherparepvec

Figure 4-14: 95% prediction interval around the modified Korn adjustment for ipilimumab OS



ipi, ipilimumab; ITT, intent-to-treat; OS, overall survival; T-VEC, talimogene laherparepvec

The modified Korn approach assumes the absence of an interaction with the treatment effect for ipilimumab in the T-VEC licensed population. The Two-step Korn assumes a potential interaction effect and is presented below. .

The two-step Korn prediction model

Development

The two-step Korn assumes a potential interaction between ipilimumab and the T-VEC licensed population (non-visceral metastatic disease).

It is noteworthy that data for ipilimumab is available for the overall population only and given that a small proportion of patients (10%) had non-visceral metastatic disease (stage IIIB-IVM1a), there is no data reported for the baseline characteristics of patients in this population with earlier stage metastatic nor are there outcomes specifically reported.

Although outcomes have not been reported specifically by stage of disease for the ipilimumab trials, HRs have been reported for subgroups according to disease stage at entry. Table 4-25 presents the HRs reported in the ipilimumab trials for the ITT population and by stage of disease. It is noteworthy that the hazard ratios for the earlier metastatic stage subgroups are based on very small number given that less than 20% of patients had earlier stage metastatic disease in these trials.

Table 4-25: Hazard ratios reported for ipilimumab RCTs for ITT and patients with earlier stage metastatic disease

	ITT	Disease stage subgroup
Ipilimumab previously treated patients	0.64 (95% CI: 0.49-0.84)	0.47* (95% CI: 0.27-0.82) Note: 10.7% of patients had earlier stage metastatic disease
Ipilimumab previously untreated patients	0.72 (95% CI: 0.59, 0.87)	0.83** Note: <20% of patients had earlier stage metastatic disease
*Hodi provided HR 0.47 for subgroup M0, M1a, Mb ** Calculated based on the weighted average of HRs for M0 and M1a reported in Robert 2011; 95% CI is not estimated CI, confidence interval; HR, hazard ratio; ITT, intent to treat; RCT, randomised controlled trial		

Methods

The aim of the two-step Korn adjustment is to obtain an estimate of ipilimumab outcomes in the stage IIIB-IVM1a disease comparable to the profile of T-VEC patients in the OPTiM trial assuming a potential interaction with treatment effect for ipilimumab using the reported hazard ratios the small subgroup of patients with earlier stage metastatic disease. The HR of 0.47 has been used in this two-step adjustment. Table 4-25 shows that the HR for ipilimumab in the earlier stage metastatic disease subgroup varies from 0.47 to 0.83. The use of HR 0.47 assigns the best possible adjustment for ipilimumab and is a conservative approach for estimating the survival gain of T-VEC versus ipilimumab.

1. Calculation of the adjustment factor and estimation of the adjusted overall survival curve for the “non-active” comparators in the ipilimumab trials, namely GP-100 (trial looking at previously treated patients) and DTIC (trial looking at previously untreated patients)

   The modified Korn equation was used as described before to determine the adjustment factor such that:

$$HR\left(\frac{TVEC_{baseline\ characteristics}}{Control\ in\ IPI\ TRIAL_{baseline\ characteristics}}\right) = \frac{HR_{TVEC_{baseline\ characteristics}}}{HR_{Control\ in\ IPI\ Trial_{baseline\ characteristics}}}$$

The calculated HRs are presented in Table 4-26.

Table 4-26: Model Coefficients and Adjustment Factors for OS and PFS adjustment of gp100 and DTIC

Treatment	HR equations	HR	Adjust-ment Factor
T-VEC (Stage IIIB-IVM1)	$\log(\widehat{HR}) = -0.154X_{Gender=} - 0.400X_{ECOG=} - 0.285X_{Visceral=0} - 0.306X_{Brain=} - 0.782X_{LDH=}$	0.18	NA
gp-100 (2nd-line)	$\log(\widehat{HR}) = -0.154X_{Gender=0.46} - 0.400X_{ECOG=0.52} - 0.285X_{Visceral=0.11} - 0.306X_{Brain=}0.85 - 0.782X_{LDH=}0.60$	0.36	0.52
DTIC (First-line)	$\log(\widehat{HR}) = -0.154X_{Gender=0.41} - 0.400X_{ECOG=0.71} - 0.285X_{Visceral=0.20} - 0.306X_{Brain=1} - 0.782X_{LDH=0.56}$	0.32	0.58
DTIC, dacarbazine; HR, hazard ratio; NA, not applicable; OS, overall survival; PFS, progression free survival; T-VEC talimongene laherparepvec			

The adjusted survival was estimated by adjusting the Kaplan Meier curve using the calculated adjustment factor to reflect outcomes in a T-VEC licensed population where 100% of the patients on T-VEC treatment had non-visceral metastatic disease:

$$S(t)_{NEW} = S(t)_{OLD}^{HR\left(\frac{T-VEC}{Control\ in\ IPI\ TRIAL}\right)}$$

2. Estimation of the survival of ipilimumab in patients with non-visceral metastatic disease similar to that of T-VEC licensed population

   As a second step, the reported HR (0.47) for ipilimumab versus gp100 in the earlier stage metastatic disease subgroup was applied to adjust outcomes to reflect outcomes for ipilimumab in this population. This assumes that the HR for ipilimumab compared to gp100 is fully adjusted and applies across different populations.

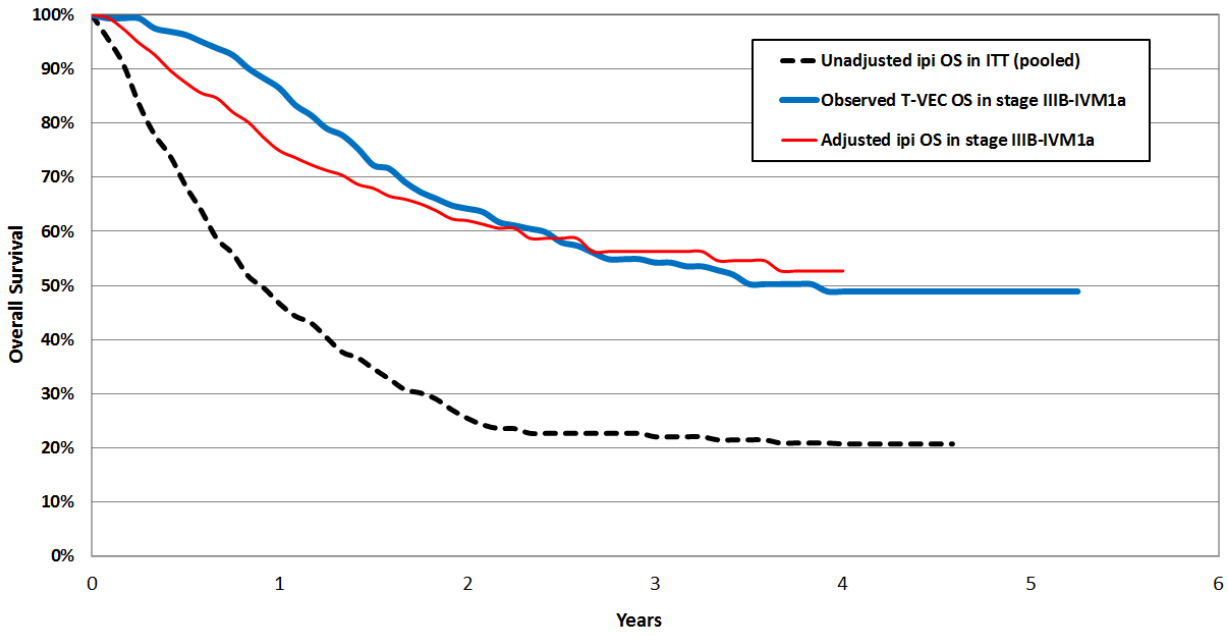
   It is noteworthy that the reported HR for ipilimumab versus gp100 in the ITT population was 0.64. It is plausible that the "true" hazard ratio for the stage IIIB-IVM1a subgroup lies in between 0.47 to 0.64. Therefore, the use of HR of 0.47 is a conservative assumption in favour of ipilimumab. The same hazard ratio of 0.47 was also applied to adjust the PFS given that there is no alternative published hazard ratio to reflect for PFS. This can be deemed to be a worst case scenario for T-VEC as the maximum adjustment is assigned to ipilimumab based on very limited evidence in the stage IIIB-IVM1a patient population.

6. Pool the two curves using the modified Mantel-Haenszel method to generate the estimated overall survival of ipilimumab.

Results

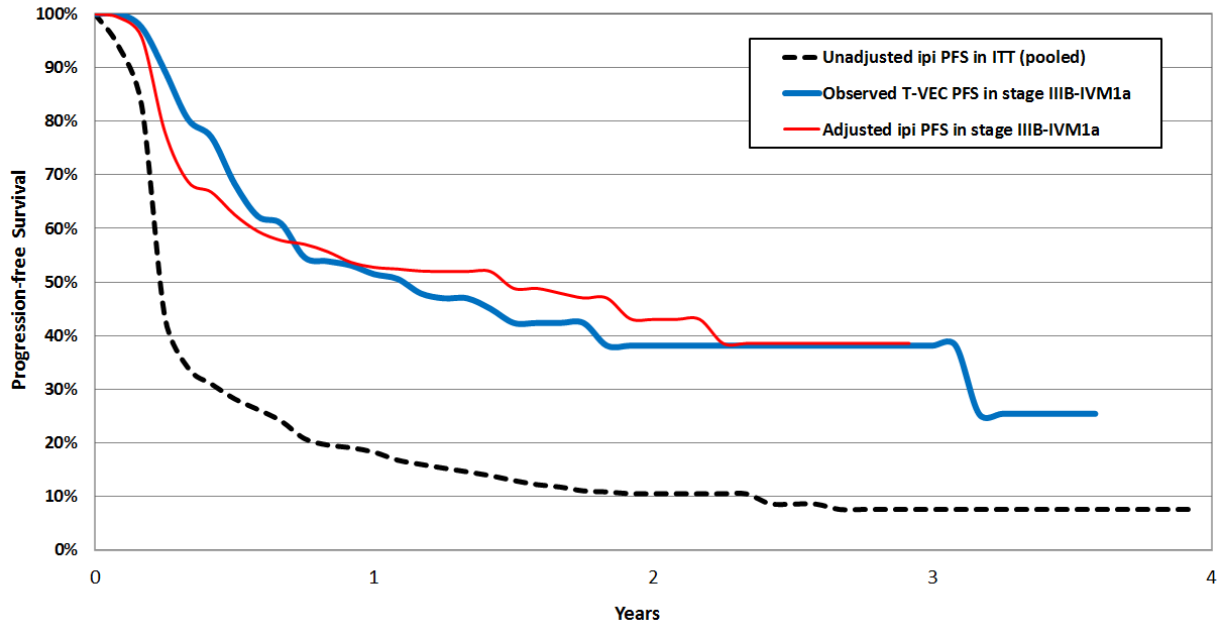
The median OS results from the meta-analysis using the two-step Korn adjustment are shown in Figure 4-15 below. The adjustment factor serves to adjust upwards the original Kaplan Meier curves such that they reflect the survival that would have been observed had ipilimumab treated a T-VEC licensed population. In addition, the adjustment factor includes an additional upward adjustment to try and capture the interaction between ipilimumab and the stage IIIB-IVM1a population. This substantially increasess the survival for ipilimumab.

Figure 4-15: Two-step Korn adjusted OS curve for ipilimumab in patients with stage IIIB-IVM1a disease



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

Figure 4-16: Two-step Korn adjusted PFS curve for ipilimumab in patients with stage IIIB IVM1a disease



ipi, ipilimumab; ITT, intent-to-treat; PFS, progression free survival; T-VEC, talimogene laherparepvec

The overall mean survival for patients with non-visceral metastatic disease (stage IIIB-IVM1a) is 6.66 years on T-VEC and 6.24 years on ipilimumab (full details of the individual curve fits and a comparison to the Kaplan Meier data can be found in Section 5). It is noteworthy that the mean life years estimated in the previous ipilimumab NICE submissions (which looked at patients across all stages of disease but with more than 80% of patients with later stage metastatic disease) was 3.29 years for previously untreated patients and 3.19 years for previously treated patients. The two-step Korn adjustment demonstrates that even in the worst case scenario T-VEC has comparable efficacy to ipilimumab.

Limitations of methodology

The modified Korn analysis assumes that differences between studies in all measured and unmeasured confounders are captured by the prediction model. The adjustment factor, which is used to "shift upwards" the overall survival curves for ipilimumab to estimate the expected survival in the T-VEC licensed population is assumed to fully represent the degree of difference in the populations.

The two-step is reliant on the magnitude of the treatment effect of ipilimumab in stage IIIB-IVM1a disease which is captured by using an estimate of the interaction effect between ipilimumab and earlier stage disease. This is most uncertain because the HR used for the two-step adjustment was taken from a subgroup of patients with earlier stage metastatic disease in the ipilimumab trial and was based on less than 10% of the ITT patient population. The most favourable HR has been ascribed to ipilimumab (0.47) given the uncertainty around these estimates (0.47 to 0.83). Therefore a full interaction effect has been assigned to ipilimumab in this two-step method, despite considerable uncertainty.

Conclusion

A NMA was not feasible given a broken network and the heterogeneity between the OPTiM trial and the comparator trials. Given the unfeasibility of conducting a NMA, the Korn model was used to estimate the efficacy of the comparators through adjusting for differences in the baseline patient characteristics to match the T-VEC arm. Given that there is no gold standard approach of dealing with the issue of broken networks, the modified Korn adjustment and the two-step adjustment method offers a plausible alternative that facilitates the comparison of the survival outcome of T-VEC with its comparators.

Survival curves were presented for ipilimumab based on the modified Korn adjustment method and two-step Korn adjustment method and for T-VEC based on the observed survival from the OPTiM RCT, in the stage IIIB-IVM1a disease population. Using the modified Korn method, there was a predicted median overall survival gain of approximately two years for T-VEC in the stage IIIB-IVM1a disease population. Using the two-step Korn method, which assumed a potential interaction effect and assigned a full interaction effect (HR=0.47) based on highly uncertain clinical evidence of subgroup data in a very small proportion of patients), T-VEC was at least comparable to ipilimumab. On the basis of these analyses, it is plausible that in the non-visceral metastatic disease population, T-VEC provides an improvement in survival over ipilimumab (modified Korn method) and at worse, is comparably effective (two-step Korn method).

4.12 Non-randomised and non-controlled evidence

Details of methods for the SLR of non-RCT evidence for treatments in advanced malignant melanoma are provided in Section 4.1.

List of relevant non-randomised and non-controlled evidence

One non-randomised study was identified by the SLR; a single-arm phase II study (Study 002/03; NCT00289016) of T-VEC that included patients with stage IIIC-IV melanoma who were not eligible for curative surgery and who had one or more tumours accessible for direct injection[115]. The study enrolled both previously untreated and previously treated patients. In total, 50 patients were enrolled: 10 with stage IIIC and 40 patients with stage IV melanoma. Half of the stage IV group had M1c visceral disease[115]. Key endpoints included ORR and OS. A summary of the methodology of the 002/03 study can be seen in Table 4-27.

Table 4-27: List of relevant non-randomised and non-controlled evidence

Trial number	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
002/03 (NCT 00289016)	Patients with injectable stage IIIC-IV who were not eligible for curative surgery	T-VEC 10^8 pfu/mL administered via intralesional injection; administered 3 weeks after initial dose(10^6 pfu/mL) then once every 2 weeks Total injection volume was up to 4 mL per treatment session	Not applicable – single arm study	Senzer N et al. J Clin Oncol 2009;27(34):5763-5771[115]	Study 002/03 provides support for the efficacy of T-VEC in the treatment of advanced or metastatic melanoma

N/A = not applicable; ORR = overall response rate; OS = overall survival; pfu = plaque forming units; T-VEC = talimogene laherparepvec

Summary of methodology of the relevant non-randomised and non-controlled evidence

Study 002/03 was a single-arm multicentre phase II trial that was conducted to assess the efficacy of T-VEC in patients with stage IIIC-IV melanoma who were not eligible for curative surgery and regardless of prior treatment[115]. Patients were initially given T-VEC at a concentration of 10^6 pfu/mL (to seroconvert HSV-seronegative patients). Subsequent doses were at 10^8 pfu/mL, given 3 weeks after the first dose, and then once every 2 weeks up to 4.0 mL per treatment session[115]. A summary of the methodology employed in the phase II study can be seen in Table 4-28.

Table 4-28: Summary of locations, trial design and methodology in Study 002/03

Trial number	002/03; NCT00289016
Location	United Kingdom and United States
Trial design	Phase II, open-label, single arm
Eligibility criteria for participants	Unresectable stage IIIC or IV melanoma
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=) and comparator(s) (n=)	T-VEC (N=50) ○ Initial dose: T-VEC 10^6 pfu/mL administered via intralesional injection ○ Subsequent doses: T-VEC 10^8 pfu/mL administered via intralesional injection; administered 3 weeks after initial dose then once every 2 weeks Total injection volume administered was up to 4.0 mL depending on the size of lesions. At first injection, tumours for injection

Trial number	002/03; NCT00289016
	needed to be at least 0.5 cm in diameter If, after eight doses, there was evidence of biologic activity (i.e., tumour inflammatory reactions and/or SD or better), treatment continued up to a maximum of 24 injections
Primary outcomes	ORR according to RECIST
Secondary/tertiary outcomes	• OS • Adverse events (according to CTCAE v3.0)
Scoring methods and timings of assessment	• Disease status was assessed at baseline, after six injections, then every 12 weeks by CT scan and clinical evaluation. Injected tumours were swabbed to detect T-VEC at 24 to 72 hours for the first 19 patients. PET/CT and ultrasound were used at the discretion of the investigator • PR categorisation required an overall tumour burden reduction of ≥30% from baseline (i.e., sum of longest diameter of all lesions). Any new lesions must have been reduced by30% from initial observation in addition to being added to the numerator for the reduction from baseline calculation • For analysis of per-protocol efficacy, patients had to have received at least four injections with tumour measurements completed up to week 9
Pre-planned subgroups	Not applicable
Duration of follow-up	Up to 47 weeks
References: Senzer et al 2009[115] CT, computed tomography, CTCAE, Common Terminology Criteria of Adverse Events; OS, overall survival; PET, positron emission tomography; pfu, plaque forming units; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; T-VEC, talimogene laherparepvec	

Statistical analysis of the relevant non-randomised and non-controlled evidence

The phase II 002/03 study was a single arm trial; therefore comparative statistical analyses were not required. Nevertheless, response rate was evaluated by using a two-stage Simon design: a response rate of ≤1% was regarded as clinically ineffective, whereas ≥10% required additional evaluation. If no responses were observed in the first 24 patients in the trial, then T-VEC would be assumed to be ineffective for advanced melanoma and the study closed. If at least one response occurred, a further 26 patients were to be enrolled. Kaplan-Meier survival curves were used to predict median and 1-year survival rates[115].

Participant flow in the relevant non-randomised and non-controlled evidence

Fifty patients were enrolled into study 002/03 from January 2006 to February 2008. The cohort comprised 10 patients with stage IIIC disease and 40 with stage IV (including 20 with M1c visceral) disease. Overall, 74% of patients had received one or more nonsurgical therapies for active disease, including dacarbazine or temozolomide and IL-2. The median follow-up during the study was 18 months (range, 11 to 36 months)[115].

Patient characteristics are summarised in Table 4-29, while patient disposition during the study is shown in Table 4-30.

Table 4-29: Characteristics of participants in the phase II 002/03 study – ITT population

Characteristic	Stage IIIC-IVM1c disease (N=50)
Age (years)	
Mean (range)	62 (34-88)
Sex, n (%)	
Male	22 (44)
Female	28 (56)
ECOG PS, n (%)	
0	31 (62)
1	19 (38)
HSV serostatus, n (%)	
Positive	36 (72)
Negative	13 (26)
Unknown	1 (2)
Disease stage, n (%)	
Stage IIIB	0 (0)
Stage IIIC	8 (16)
Stage IVM1a	15 (30)
Stage IVM1b	5 (10)
Stage IVM1c	20 (40)
Missing	2 (4)
LDH, n (%)	
≤ULN	35 (70)
>ULN	12 (24)
Missing	3 (6)
Prior therapy*, n (%)	
None	13 (26)
Chemotherapy†	25 (50)
Immunotherapy‡	22 (44)
Other§	6 (12)
No. of prior therapies	
0	13 (26)
1	13 (26)
2	8 (16)
≥3	16 (32)

References: Senzer et al 2009[115]

ECOG, Eastern Cooperative Oncology Group; HSV, herpes simplex virus; LDH, lactate dehydrogenase; ULN, upper limit of normal;

Characteristic	Stage IIIC-IVM1c disease (N=50)
* Excludes surgery, radiation, or adjuvant therapy. Categories are not mutually exclusive † Includes regional therapy ‡ Includes vaccine, anti– cytotoxic T-cell lymphocyte-4, and cytokine therapy § Includes cryotherapy and imiquimod	

Table 4-30: Patient disposition during study 002/03

	Details
Disease stage	IIIC-IVM1c
Efficacy population, n	50
Discontinued from treatment, n (%)	0 (0)
Discontinued from study, n (%)	37 (74)
Median duration in study, months (range)	13.2 (1-39)
Stratification factors	Not applicable
References: Amgen data on file[80]	

Quality assessment of the relevant non-randomised and non-controlled evidence

To assess concerns around bias and generalisability of the phase II 002/03 study, quality assessment has been carried out according to guidance that has been published in 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)'[83]. Critical appraisal of the OPTiM study is shown in Table 4-31.

Table 4-31: Quality assessment of the phase II 002/03 study

Study question	Further details on how the question is addressed in the study	Short response
Was randomisation carried out appropriately?	The study was a single arm trial	n/a
Was the concealment of treatment allocation adequate?	Not applicable – only T-VEC was administered to patients	n/a
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The study was a single arm trial	n/a

Study question	Further details on how the question is addressed in the study	Short response
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The study was a single arm trial	n/a
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest that the study authors measured more outcomes than they reported	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were based on the ITT. All patients who entered the study (N=50) were eligible for analysis	Yes
References: Senzer et al 2009[115] ITT, intent to treat; n/a, not applicable; T-VEC, talimogene laherparepvec		

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

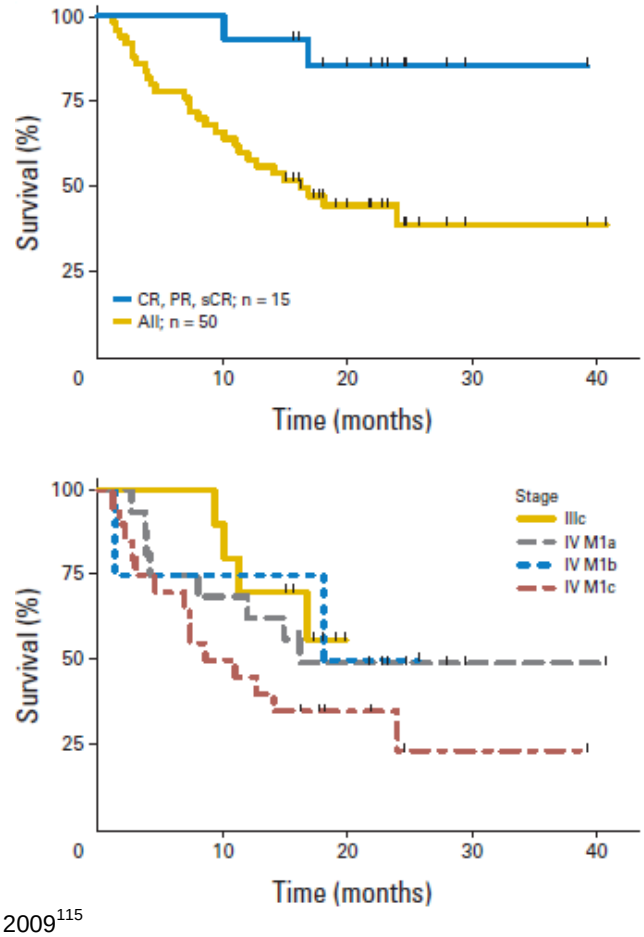
Primary endpoint: ORR

During the phase II study, the ORR was 26% (n=13) in all patients. This included 8 patients with CR and 5 with PR. Twelve of those individuals with objective systemic responses continued for more than 6 months (range 7 to 31). Response onset ranged from 2 to 10 months after the first dose[115]. These findings were in line with the ORR that was observed in the ITT population of the OPTiM study following treatment with T-VEC (see Appendix 1.4).

Secondary endpoint: OS

Treatment with T-VEC for all patients in study 002/03 resulted in median OS that was greater than 16 months and 1-year survival of 58%[115]. The 1-year survival rate for those patients that achieved either CR, PR or surgical CR (n=15) was 93% (Figure 4-17)[115].

Figure 4-17: Kaplan-Meier curves for OS during study 002/03 stratified by response type (top) or disease stage (bottom)



References: Senzer et al 2009[115]
CR, complete response; OS, overall survival; PR, partial response

Secondary endpoint: adverse events

In total, 85% of patients had T-VEC-related AEs which were all grades 1 to 2 in severity. AEs that were observed in three or more patients were associated with a mild influenza-like syndrome. Specifically these were[115]:

- fever (52%)
- chills (48%)
- fatigue/malaise (32%)
- nausea (30%)
- vomiting (20%)
- headache (20%).

AEs of grade 3 severity were infrequent: six patients experienced pain that was potentially related to the underlying disease; four patients each experienced fatigue and dyspnoea. There were 21 severe AEs, all of which were considered unrelated to T-VEC therapy[115].

4.13 Adverse reactions

In a similar manner to efficacy outcomes, safety data from the OPTiM study are presented for patients with stage IIIB-IVM1a disease, as this is the relevant indication being sought from the regulatory authorities. Data for the overall safety population in the OPTiM study are not presented here, but were reflective of those seen in patients with stage IIIB-IVM1a disease.

All AEs

The incidence of all treatment-emergent AEs experienced by patients with stage IIIB-IVM1a disease in the OPTiM study was higher in the T-VEC treatment group (99%) compared with the GM-CSF treatment group (93%). Similarly, the incidences of (serious adverse events) SAEs and treatment-related AEs were higher in the T-VEC treatment group compared to the GM-CSF treatment group (20% vs 13% and 93% vs 79%, respectively). Treatment-emergent AEs leading to discontinuation from the OPTiM study were comparable between the T-VEC treatment group (9%) and GM-CSF treatment group (7%) and only one fatal AE occurred during the study (one patient in the T-VEC treatment group, though this was not related to treatment). A summary of all AEs can be seen in Table 4-32[80].

Table 4-32: Summary of treatment-emergent AEs in patients with stage IIIB-IVM1a disease (safety population)

	Stage IIIB-IVM1a disease	
	T-VEC (N=163)	**GM-CSF (N=76)**
All treatment-emergent AEs (%)	99	93
Worst grade of 1	26	40
Worst grade of 2	41	30
Worst grade of 3	28	22
Worst grade of 4	4	1
Worst grade of 5	1	0
All treatment-emergent SAEs (%)	20	13
Worst grade of 1	1	0
Worst grade of 2	3	3
Worst grade of 3	13	9
Worst grade of 4	4	1
Worst grade of 5	1	0
Treatment-related emergent AEs (%)	93	79
Worst grade of 1	38	57
Worst grade of 2	42	17
Worst grade of 3	12	5
Worst grade of 4	2	0
Worst grade of 5	0	0
Treatment-related emergent SAEs (%)	6	0
Worst grade of 1	0	0

	Stage IIIB-IVM1a disease	
	T-VEC (N=163)	**GM-CSF (N=76)**
Worst grade of 2	2	0
Worst grade of 3	3	0
Worst grade of 4	2	0
Worst grade of 5	0	0
Study treatment discontinuation due to treatment-emergent AEs (%)	9	7
Study treatment discontinuation due to treatment-related AEs (%)	2.5	-
Fatal AEs on study (%)	1	0

Reference: Amgen data on file[80] ENREF 83; Harrington et al 2015[82]
AE = adverse event; GM-CSF = granulocyte macrophage colony-stimulating factor; SAE = serious adverse event; T-VEC = talimogene laherparepvec

Common treatment-emergent AEs

A summary of treatment-emergent AEs that occurred at an incidence of ≥5% in any treatment group in patients with stage IIIB-IVM1a disease can be seen in Table 4-33[80] ENREF 83. Treatment-emergent AEs that occurred with a higher incidence (>5%) in the T-VEC treatment group compared with the GM-CSF treatment group included fatigue (50.9% vs 36.8%, respectively), chills (49.7% vs 7.9%), pyrexia (39.9% vs 10.5%), nausea (33.7% vs 21.1%), influenza like illness (33.7% vs 9.2%), injection site pain (30.1% vs 6.6%), vomiting (18.4% vs 9.2%), diarrhoea (21.5% vs 9.2%), headache (16.6% vs 1.2%), myalgia (18.4% vs 5.3%), arthralgia (16.6% vs 6.6%), pain in extremity (17.8% vs 7.9%), constipation (12.3% vs 1.3%), cellulitis (6.7% vs 1.3%) (Table 4-33)[80].

The majority of patients reported treatment-emergent AEs of grade ≤3. The proportion of patients who reported grade 4 and grade 5 AEs was 4% vs 1% and 1% vs 0% for the T-VEC and GM-CSF treatment groups, respectively (Table 4-32).

Table 4-33: Summary of treatment-emergent AEs in patients with stage IIIB-IVM1a disease (safety population)

Preferred term	**Stage IIIB-IVM1a disease**			
AE[a]	**T-VEC (N=163)**		**GM-CSF (N=76)**	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Fatigue	50.9	1.8	36.8	1.3
Chills	49.7	0	7.9	0
Pyrexia	39.9	0	10.5	0
Nausea	33.7	0.6	21.1	0
Influenza like illness	33.7	0.6	9.2	0
Injection-site pain	30.1	1.8	6.6	0

Preferred term	Stage IIIB-IVM1a disease			
AE[a]	T-VEC (N=163)		GM-CSF (N=76)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Diarrhoea	21.5	0.6	9.2	0
Vomiting	18.4	1.2	9.2	0
Myalgia	18.4	0.6	5.3	0
Pain in extremity	17.8	2.5	7.9	0
Pain	17.2	0.6	11.8	1.3
Headache	16.6	1.2	9.2	0
Arthralgia	16.6	0.6	6.6	0
Constipation	12.3	0	1.3	0
Rash	12.3	0.6	5.3	0
Dizziness	11.7	0	1.3	0
Upper respiratory tract infection	11.7	0	7.9	0
Oedema peripheral	8.6	0.6	10.5	2.6
Pruritus	8.6	0	15.8	0
Decreased appetite	7.4	0	11.8	0
Injection-site erythema	6.1	0	21.1	0
Injection site reaction	3.7	0	13.2	0
Dyspnoea	1.8	0.6	9.2	2.6

Reference: Amgen data on file[80] _ENREF_83

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

[a] Treatment-emergent AEs by preferred term of any grade with incidence ≥10% in either arm and/or grade 3 to 4 AEs with incidence of ≥2% in either arm.

Common treatment-related AEs

Table 4-34 provides a summary of the incidence rates of treatment-related AEs. The incidence rates of treatment-related grade 3/4 AEs are very low with no grade 3/4 AE occurring in more than 2% of patients. Fatigue was the most frequent treatment-related grade 3/4 AE associated with T-VEC, which occurred in 1.8% of patients.

Table 4-34: Summary of treatment-related AEs in patients with stage IIIB-IVM1a disease (safety population)

Preferred term	Stage IIIB-IVM1a disease			
AE[a]	T-VEC (N=163)		GM-CSF (N=76)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Chills	49.1	0	3.9	0
Fatigue	44.8	1.8	31.6	0
Pyrexia	38.0	0	7.9	0
Influenza like illness	33.7	0.6	9.2	0
Injection-site pain	28.2	1.2	6.6	0
Nausea	25.2	0.6	11.8	0
Myalgia	17.2	0.6	5.3	0
Pain	14.7	0.6	9.2	0
Vomiting	12.9	0.6	5.3	0
Headache	12.9	0.6	7.9	0
Arthralgia	12.9	0.6	5.3	0
Diarrhoea	10.4	0	5.3	0
Pruritus	6.7	0	11.8	0
Injection-site erythema	6.1	0	19.7	0
Injection site reaction	3.7	0	11.8	0

Reference: Amgen data on file[80] ENREF 83

Abbreviations: AE, adverse event; GM-CSF, granulocyte macrophage colony stimulating factor; T-VEC, talimogene laherparepvec.

[a] Treatment-emergent AEs by preferred term of any grade with incidence ≥10% in either arm and/or grade 3 to 4 AEs with incidence of ≥2% in either arm.

SAEs

The incidence of SAEs that occurred in patients with stage IIIB-IVM1a disease in the OPTiM study can be seen in Table 4-35[80].

Table 4-35: Summary of treatment-emergent SAEs in patients with stage IIIB-IVM1a disease (safety population)

	Stage IIIB-IVM1a disease	
	T-VEC (N=163)	GM-CSF (N=76)
All treatment-emergent SAEs (%)	20.2	13.2
Worst grade of 1	0.6	0
Worst grade of 2	2.5	2.6
Worst grade of 3	12.9	9.2
Worst grade of 4	3.7	1.3
Worst grade of 5	0.6	0

Reference: Amgen data on file[80] ENREF 83

	Stage IIIB-IVM1a disease	
	T-VEC (N=163)	GM-CSF (N=76)
GM-CSF, granulocyte macrophage colony-stimulating factor; SAE, serious adverse event; T-VEC, talimogene laherparepvec		

AEs leading to discontinuation

The incidence of treatment-emergent AEs leading to discontinuation in patients with stage IIIB-IVM1a disease in the OPTiM study can be seen in Table 4-36[80]. The rate of study drug discontinuation in the T-VEC arm due to any grade treatment-related AEs was low at 2.5% in patients with stage IIIB-IVM1a disease.

Table 4-36: Summary of treatment-emergent AEs leading to discontinuation of study treatment in patients with stage IIIB-IVM1a disease (safety population)

	Stage IIIB-IVM1a disease	
	T-VEC (N=163)	GM-CSF (N=76)
Study treatment discontinuation due to treatment emergent AEs (%)	8.6	6.6
Reference: Amgen data on file[80] AE, adverse event; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec		

Fatal AEs

The incidence of treatment-emergent fatal AEs in patients with stage IIIB-IVM1a disease in the OPTiM study can be seen Table 4-37[80]. No treatment-related AEs were observed in the OPTiM study[80].

Table 4-37: Summary of treatment-emergent fatal AEs in patients with stage IIIB-IVM1a disease (safety population)

	Stage IIIB-IVM1a disease	
	T-VEC (n=163)	GM-CSF (N=76)
Fatal AEs on study (%)	0.6	0
Reference: Amgen data on file[80] AE, adverse event; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec		

Summary of comparative safety data for the relevant comparators

An overview of the key AEs that are associated with ipilimumab, vemurafenib and dabrafenib as reported during pivotal clinical trials is shown in Table 4-38. Ipilimumab is most commonly associated with AEs resulting from increased or excessive immune activity. Furthermore, treatment with ipilimumab is associated with a number of grade 3 or 4 AEs, which may involve the gastrointestinal, liver, skin, nervous, endocrine, ocular, or other organ systems[47]. The most common adverse AEs (i.e. >30% of patients) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. Cutaneous

squamous cell carcinoma was very commonly reported and was most commonly treated by local excision[48]. The most frequently occurring AEs (i.e. ≥15 % of patients) reported with dabrafenib use are hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting[49].

Table 4-38: Key adverse events and dose discontinuations and/or modifications due to overall or treatment-related toxicities during pivotal trials with ipilimumab, vemurafenib and dabrafenib

Drug (Trial)	AEs	Dose discontinuations and/or modifications due to toxicities (treatment-emergent or treatment-related)
Ipilimumab (MDX010-20)[72]	Grade 3 or 4 drug-related AEs in 23% of patients in the ipilimumab arm; most of these AEs were immune-related.	Ipilimumab therapy was discontinued for adverse reactions in 10% of patients
Vemurafenib (BRIM-3)[90]	Grade 3 or 4 treatment-related AEs in 43% of patients in the vemurafenib group including 18% of grade 3 SCC/keratoacanthoma.	38% of patients required dose modification or interruption because of toxic effects, and AEs led to discontinuation of study drug in 7% of patients
Vemurafenib (BRIM-2)[71]	26% developed grade 3 SCC/keratoacanthoma	45% of patients required dose reduction and 64% required dose interruption because of toxicities
Dabrafenib (BREAK-3)[98]	Grade 3 or 4 AEs occurred in 33% of dabrafenib treated patients including SCC (7%), pyrexia (5%), and hand-foot syndrome (2%)	Dabrafenib dose reduction was required in 28% of patients because of toxic effects, and AEs led to discontinuation of study drug in 3% of patients
AE, adverse event; SCC, squamous cell carcinoma		

4.14 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence (clinical benefits and harms)

OPTiM RCT: T-VEC versus GM-CSF

- The key clinical evidence for T-VEC comes from the OPTiM study, which was a phase III, randomised, open-label, active-controlled, multicentre study evaluating the efficacy and safety of T-VEC compared to GM-CSF in 436 patients with unresectable, stage IIIB/c and stage IV malignant melanoma[79]. An exploratory subgroup analysis of patients with stage IIIB-IVM1a disease (which aligned with the proposed licensed indication for T-VEC in non-visceral metastatic disease) was conducted. This consisted of 57% of the ITT population (N= 249). There was no head-to-head RCT evidence comparing T-VEC with any of the relevant comparators defined in the decision problem.
- In the analysis of patients with stage IIIB-IVM1a malignant melanoma (N=249[80]:
  - The complete response rate (CR) was 16.6% in the T-VEC arm and 0.0% in the GM-CSF arm (P<0.001) (i.e., 1 in 6 patients treated with T-VEC achieved CR in this population).
  - The overall response rate (ORR) (CR + PR) was 40.5% in the T-VEC arm versus 2.3% in the GM CSF arm (P<0.0001) in the main phase of the study

- The ORR results achieved with T-VEC were generally durable; with the durable response rate (DRR) 25.2% in the T-VEC arm versus 1.2% in the GM-CSF arm (odds ratio [OR] was 28.6 [95% CI: 3.9, 211.5]; P<0.0001)
- Among patients who achieved a DR, the survival rate at 3 years was 95% and at 4 years was 87%. In addition to improved OS, achieving DR was associated with reduced risk of initiating subsequent systemic therapy: HR (DR vs no DR) = 0.33 (95% CI: 0.17-0.65), P=0.0007 and patients with a DR had a higher quality of life improvement rates vs patients with no DR: odds ratio (DR vs no DR) = 2.8 (95% CI: 1.1-7.0), P=0.0247.
- T-VEC also produced a median OS gain of 25.3 months versus GM-CSF (46.8 vs 21.5 months, p=0.0008 in the final data cut).
- An open-label phase II clinical trial (Study 002/03) also demonstrated efficacy outcomes that were in line with the OPTiM study[115].

- Treatment related adverse events (AEs) with T-VEC were generally mild and reversible. Few patients discontinued because of toxicity. The most common AEs were flu-like symptoms (including fatigue, chills, and pyrexia). The only grade 3 or 4 AE occurring in >2% of T-VEC–treated patients was cellulitis; there were no treatment-related deaths[79]. This toxicity profile compares favourably to the other treatment options, especially ipilimumab, which is commonly associated with immune-related AEs (particularly diarrhoea and colitis), which can be fatal.

Results of indirect comparisons of survival outcomes: T-VEC versus ipilimumab

- In the absence of relevant head-to-head RCT evidence, efforts were made to conduct a NMA to evaluate T-VEC versus relevant comparators. The broad evidence base identified by the SLR showed that the OPTiM study was an isolated trial, with no common comparator linking to other published trials or publicly available data.
- In order to present and describe the key clinical evidence relevant to the decision problem, further inclusion/exclusion criteria were applied to identify those phase III RCTs which evaluated interventions/comparators defined in the scope, as monotherapy, for the treatment of patients with stage IIIB-IV melanoma.
  - Ten phase III RCTs (including OPTiM) were identified; T-VEC (1), ipilimumab (4), vemurafenib (3) and dabrafenib (2) as a monotherapy. All ten RCTs reported efficacy for the broad population of patients with stage III-IV metastatic melanoma. However only OPTiM reported efficacy for the stage IIIB-IV1a population, which comprised 57% of patients, compared with only11-17%, for ipilimumab, 18%-23% with vemurafenib and 16% and 20% for dabrafenib. Given the challenges of both a disconnected network and the significant differences in disease stage of the patient populations, it was concluded that a NMA was not feasible.
  - Survival curves were presented for ipilimumab based on the modified Korn adjustment method and two-step Korn adjustment method and for T-VEC based on the observed survival from the OPTiM RCT, in the stage IIIB-IVM1a disease population. Using the modified Korn method, there was a predicted median overall survival gain of approximately two years for T-VEC in the stage IIIB-IVM1a disease population. Using the two-step Korn method, which assumed a potential interaction effect and assigned a full interaction effect (HR=0.47) based on highly uncertain clinical evidence of subgroup data in a very small proportion of patients), T-VEC was at least comparable to ipilimumab.

- On the basis of these analyses, it is plausible that in the non-visceral metastatic disease population, T-VEC provides an improvement in survival over ipilimumab (modified Korn method) and at worse, is comparably effective (two-step Korn method).

Strengths of T-VEC clinical evidence in the treatment of patients with regionally or distantly metastatic melanoma with no visceral disease

T-VEC was studied in a large, phase III, prospective, randomised clinical trial that included a large group of patients with non-viseral metastatic disease (stage IIIB-IVM1a disease), in which existing therapies have not been extensively studied. The results from the OPTiM study show that T-VEC consistently demonstrated clinically significant improvements in efficacy measures across primary and secondary endpoints. T-VEC also demonstrated improvement in durable and complete responses, and clinically significant and meaningful survival benefit[79]. Findings which were supported by an open-label phase II clinical trial (Study 002/03)[115]. Finally the OPTiM trial reported a CR rate of 16.6% in the T-VEC arm compared to 0.0% in the GM-CSF arm (P<0.001) in patients without visceral disease (i.e., 1 in 6 patients treated with T-VEC achieved CR in this population)[79]. The high CR rate is an important finding because it has been demonstrated that CR is strongly associated with long-term survival[46].

The evidence from the OPTiM study is generalizable to UK clinical patients. The UK was one of the four trial sites for OPTiM study[79]. The study enrolled subjects with stage IIIB, IIIC, or IV malignant melanoma that was not surgically resectable. Enrolment of subjects with stage IV M1c disease was limited to no more than 40% of the total subjects in each treatment arm. Prior nonsurgical melanoma treatment other than adjuvant therapy was allowed, but not required; thus, the OPTiM Study 005/05 enrolled both subjects who had received prior systemic treatment and those who had not[79]. These eligibility criteria allowed for enrolment of a broadly representative population with metastatic melanoma. The trial population was generalizable to the UK population of patients with metastatic melanoma: 57.3% were men, 97.9% were white, and the mean age was 63 years. In Study 002/03, 44% were men, 96% were white, and the mean age was 63 years[115]. These results are qualitatively consistent with the epidemiologic data that shows that median age is 61 years at diagnosis and that melanoma occurs more frequently in subjects who are white compared with subjects who are non-white[116,117].

The limitations of the comparative effectiveness evidence in the treatment of patients with non-visceral metastatic melanoma

GM-CSF, the comparator in the OPTiM phase III study, is not licensed or recommended for melanoma. The SLR showed that GM-CSF had not been evaluated as a monotherapy against any of the defined comparators for the treatment of metastatic melanoma. Therefore the OPTiM trial was isolated, with no common comparator with other published trials or publically available data and therefore could not be linked to an evidence network with any comparators, thus making a traditional NMA unfeasible. Evidence for the stage IIIB-IVM1a disease population, aligned with the anticipated T-VEC indication, was only reported for the T-VEC study OPTiM (accounting for 57% of ITT patient population). However there was minimal data reported by disease stage for the comparators, eg for ipilimumab, where the

earlier stage metastatic disease accounted for only 11%-17% of the ITT population and outcomes were not reported for this population.

Assessment of comparative effectiveness for T-VEC versus the defined comparators using a NMA was rendered unfeasible by a disconnected network of evidence and the heterogeneity of the RCT patient population with regards metastatic disease stage (there was minimal data on effectiveness for comparators in the T-VEC-licensed population). The modified Korn and two-step Korn approaches were used in an attempt to overcome these limitations. The modified Korn analysis assumes the absence of a potential interaction effect between ipilimumab treatment and stage IIIB-IVM1a disease, and may be an underestimate of the treatment effect for ipilimumab. The two-step Korn analysis, assumed an interaction effect between ipilimumab treatment and the stage of metastatic disease. However, the magnitude of the interaction effect was based on the best possible estimate of effect (HR 0.47) for ipilimumab based on a subgroup analysis, subject to considerable uncertainty, where stage IIIB-IVM1a patients formed only 10.7% of the ITT population.

Discussion

Although the treatment paradigm in melanoma continues to expand, with recently licensed treatments rapidly becoming the new standard of care, there is still significant unmet need: Current treatments show a lack of durable response, low complete response rates and a toxicity profile that may not be well tolerated. In addition, for patients with non-visceral metastatic disease, the evidence base for existing therapies is minimal; with no evidence to show that treatments can delay progression to visceral disease and improve survival. Therefore for these patients there remains a need for effective, well tolerated therapies that provide both high and durable response rates and delay/prevent progression to visceral disease, in order to deliver long term survival benefit for patients with this serious, life-threatening disease.

T-VEC is a novel oncolytic immunotherapy that has been recognised by the EMA as an innovative first-in-class advanced therapy medicinal product (ATMP) derived from a virus. It has a unique dual mechanism of action that produces local tumour control as well as systemic anti-tumour immune responses. In an analysis of patients with non-visceral metastatic disease (stage IIIB-IVM1a), T-VEC demonstrated a clinically significant and meaningful improvement in OS, in addition to high and durable rates of response (CR and DRR) and a highly favourable safety profile.

Patients with non-visceral metastatic disease are routinely treated with immunotherapies rather than BRAF inhibitors (except where there is evidence of rapidly progressing disease). Ipilimumab is therefore the clinically relevant comparator for this submission. The evidence for T-VEC from OPTiM and the adjusted estimates of survival for ipilimumab indicate that it is plausible that T-VEC provides an improvement in survival over ipilimumab and is at worse, comparable. Although ipilimumab has shown extended survival in a proportion of patients, this was not reflected by the low CR rates reported (1.5%)[72], and suggests a delayed response. Whilst T-VEC shows extended long term survival, importantly it has also demonstrated high (and durable) CR rates (16.6%), with no evidence of the delayed response observed with ipilimumab.

In addition, Ipilimumab treatment is associated with a range of treatment limiting and potentially fatal immune-related adverse events[47,73,74], which are of particular concern for those with earlier stage metastatic disease (IIB-IVM1a), whilst T-VEC has a highly favourable safety profile with treatment related adverse events generally mild and reversible (only one grade 3 or 4 adverse event, cellulitis, occurring in 2.1% of T-VEC–treated patients).

T-VEC therefore addresses the unmet need in patients with non-visceral metastatic disease, providing a high and durable response rate, a long term survival benefit, combined with an improved safety profile.

The management of advanced melanoma is rapidly evolving, with the emergence of further systemic therapies (e.g. BRAF inhibition in combination with MEK inhibition, and anti CTLA4 therapy potentially in combination with anti-PD1 therapy). Although there is uncertainty about how these treatments will be sequenced in the future, it is expected that treatments such as T-VEC will still be of value for the specific target population of patients with limited metastatic disease and readily injectable disease.

Conclusion

For patients with non-visceral metastatic disease (stage IIIB, IIIC and IVM1a), there is evidence of improved or, at least, comparative efficacy for T-VEC versus ipilimumab, combined with a very favourable safety profile. T-VEC is therefore a valuable treatment option for patients with non-visceral metastatic disease, to delay and/or prevent progression to later stages of disease and improve OS.

4.15 Ongoing studies

Table 4-39: Summary of ongoing studies expecting to report within the next 12 months

Trial No	Description	Interventions	Population	Primary Outcome Measure	Date Expected to Report
20120324	A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of T-VEC in Subjects With Unresected, Stage IIIB to IVM1c Melanoma	Initial dose of T-VEC is up to 4.0 mL of 10^6 PFU/mL. Second dose up to 4.0 mL of 10^8 PFU/mL will be 21 (+5) days after initial dose. Subsequent doses will be every 14 (±3) days.	Male or female ≥ 18yrs with histologically confirmed diagnosis of melanoma and unresected stage IIIB-IV regardless of prior line of therapy	Proportion of subjects with detectable T-VEC DNA in the blood and urine any time after administration within the first 3 cycles	**Primary Analysis for Biodistribution-8/30/2016**

Trial No	Description	Interventions	Population	Primary Outcome Measure	Date Expected to Report
20120325	A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with T-VEC	Initial dose of T-VEC is up to 4.0 mL of 10^6 PFU/mL. Second dose up to 4.0 mL of 10^8 PFU/mL will be 21 (+5) days after initial dose. Subsequent doses will be every 14 (±3) days	Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVMIc melanoma for whom surgery is not recommended	Correlation between baseline intratumoral CD8+ cell density and ORR in subjects with unresected stage IIIB to IVM1c melanoma treated with T-VEC	**Interim Analysis for Response Rate - 10/26/2016** Primary Analysis for Efficacy Primary Endpoint - 3/12/2018
20110264	A Phase 1b/2, Multicenter, Open-label Trial to Evaluate the Safety and Efficacy of T-VEC and Ipilimumab Compared to Ipilimumab Alone in Subjects With Unresected, Stage IIIB-IV Melanoma	Initial dose of T-VEC is up to 4.0 mL of 10^6 PFU/mL. Second dose up to 4.0 mL of 10^8 PFU/mL will be 21 (+5) days after initial dose. Subsequent doses will be every14 (±3) days. Ipilimumab 3mg/kg will be administered every 3 weeks for 4 cycles.	Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVMIc melanoma for whom surgery is not recommended.	Phase 1b: Safety and tolerability of talimogene laherparepvec in combination with ipilimumab Phase 2: Efficacy as assessed by confirmed objective response rate with T-VEC in combination with ipilimumab versus ipilimumab	**Primary Analysis for Phase 2 Primary Endpoint - 7/26/2016**
20110265	A Phase 1b/3, Multicenter, Open-label Trial of T-VEC in Combination With Pembrolizumab (MK-3475) for Treatment of Unresected, Stage IIIB to IVM1c Melanoma (MASTERKEY-265)	Initial dose of T-VEC is up to 4.0 mL of 10^6 PFU/mL. Second dose up to 4.0 mL of 10^8 PFU/mL will be 21 (+5) days after initial dose. Subsequent doses will be every 14 (±3) days. Pembrolizumab 200mg will be administered every 3 weeks.	Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVMIc melanoma for whom surgery is not recommended.	Phase 1b: Safety and tolerability of T-VEC in combination with Pembrolizumab Phase 3: Efficacy as assessed by PFS (central review by RECIST 1:1) and OS with T-VEC in combination with Pembrolizumab versus Pembrolizumab	**Primary Analysis for Efficacy in Phase 1- 1/14/2016** **Interim Safety Analysis in Phase 3 - 10/19/2016** Primary Analysis for PFS in Phase 3 - 7/19/2016

DNA, deoxyribonucleic acid; ORR, objective rate response; OS, overall survival; PFU,plaque forming units; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors; T-VEC, talimogene laherparepvec

5 Cost-effectiveness

- A de novo cost-effectiveness partitioned survival model was developed for the economic evaluation and undertaken in accordance with the NICE reference case. A lifetime analysis was performed (cycle length of one week; half-cycle correction used). Costs and outcomes were discounted at 3.5% per annum
- The population considered in the model was in accordance with the anticipated license; unresectable regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease (i.e. patients with disease stages IIIB - IVM1a)
- The baseline prognostic characteristics for ipilimumab were adjusted to match the anticipated licensed patient population of T-VEC
- Drug acquisition costs were taken from the Brisith National Formulary, AE costs were based on previous NICE submissions in melanoma, inflated to present year as well as an Amgen conducted cost of AE's study
- Health state utilities were based on a recent NICE Technology Appraisal in melanoma (TA329)
- Parameter uncertainty was assessed in a series of scenario analyses, deterministic sensitivity analyses and probabilistic sensitivity analysis
- Base case deterministic results based on anticipated list price for T-VEC and NHS list price for ipilumumab show that the incremental cost per QALY gained for T-VEC compared to ipilimumab is between [redacted]
- In the analyses using the modified Korn method and comparing T-VEC with ipilimumab in a range of potential PAS discounts for ipilimumab, T-VEC remained a cost-effective strategy (below a threshold of £30,000 per QALY gained) when the discount for ipilimumab was increased up to 55%. For the two-step Korn method, the ICER remained below £30,000 per QALY when the discount for ipilimumab was increased up to 10%
- The cost-effectiveness results were robust to a number of scenario analyses, univariate sensitivity analyses and probabilistic sensitivity analysis conducted to assess uncertainty

5.1 Published cost-effectiveness studies

Identification of studies

A SLR was conducted in September 2015 to systematically identify, critically review, and summarise studies evaluating the cost-effectiveness of treatments in advanced melanoma. The literature review was subsequently used to inform the cost-effectiveness model structure and some of the key inputs used in this appraisal.

Search strategy

The search included peer-reviewed journal articles, HTA documents, and data from relevant conference proceedings. Full details are provided in Appendix 1.2. The following databases were searched for relevant studies:

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.

- EconLit (OvidSP):1886 to August 2015
- NHSEED (OvidSP):2nd Quarter 2015

Supplementary searches were undertaken for the following trials registers from inception to March 2015:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- EU Clinical Trials Register (EUCTR) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- PharmaNet.Bund (http://www.pharmnet-bund.de/static/de/index.html)
- National Institutes of Health (NIH) Clinical Trial Registry (CTR)
- Australian New Zealand Clinical Trials Registry (ANZCTR) (http://www.anzctr.org.au/TrialSearch.aspx)

Further supplementary searches were undertaken in relevant conference abstracts from 2013 to present:

- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(http://www.ispor.org/)
- European Association of Dermato Oncology (EADO) (http://www.eado.org/)
- European Cancer Congress (ECC) (http://www.esmo.org/Conferences/European-Cancer-Congress-2015)
- Society of Melanoma Research (SMR) (http://www.societymelanomaresearch.org/)
- Perspectives in Melanoma (PIM) (http://imedex.com/perspectives-melanoma-conference/)

Additionally, a manual search of HTA websites was also under taken for the:

- UK:
  - NICE (www.nice.org.uk)
  - AWMSG (http://www.awmsg.org/app/search?execution=e1s1)
  - SMC (http://www.scottishmedicines.org.uk/Home)
- Canada
  - CADTH (http://www.cadth.ca)

Study selection

Study inclusion was not limited by language, HTA assessments were restricted to the UK (England, Scotland and Wales) and Canada (which hasa similar HTA jurisdiction to the UK), and the publication date for conference proceedings was limited to 2013. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 5-1. Of the 51 studies that were identified and extracted in full, 36 were conducted in patients with stage III to IV melanoma and 15 studies in patients with any stage melanoma.

Of the identified studies, 42 studies reported information on the type of analysis which included cost-utility analysis (n=24), cost-effectiveness analysis (n=12) and both cost-utility and cost-effectiveness studies (n = 6). The model design was reported in 30 studies which

included Markov models (n=14), partitioned-survival models (n=7), semi-Markov models (n=3), decision-analytical models (n=3), survival analysis models (n=2), and a budget impact calculator (n=1).The time horizons investigated in the models ranged from 1 to 40 years and the main cycle length reported ranged from weekly (advanced melanoma) to monthly (any stage melanoma).

Although 51 studies were identified in the SLR only 11 were deemed relevant to the decision problem (Table 5-2) in that they included a relevant comparator as defined in the final scope (T-VEC, ipilimumab, vemurafenib or dabrafenib) and was applicable with regards to the decision making process in a UK HTA setting (in terms of NICE reference case).

Table 5-1: Study inclusion and exclusion criteria

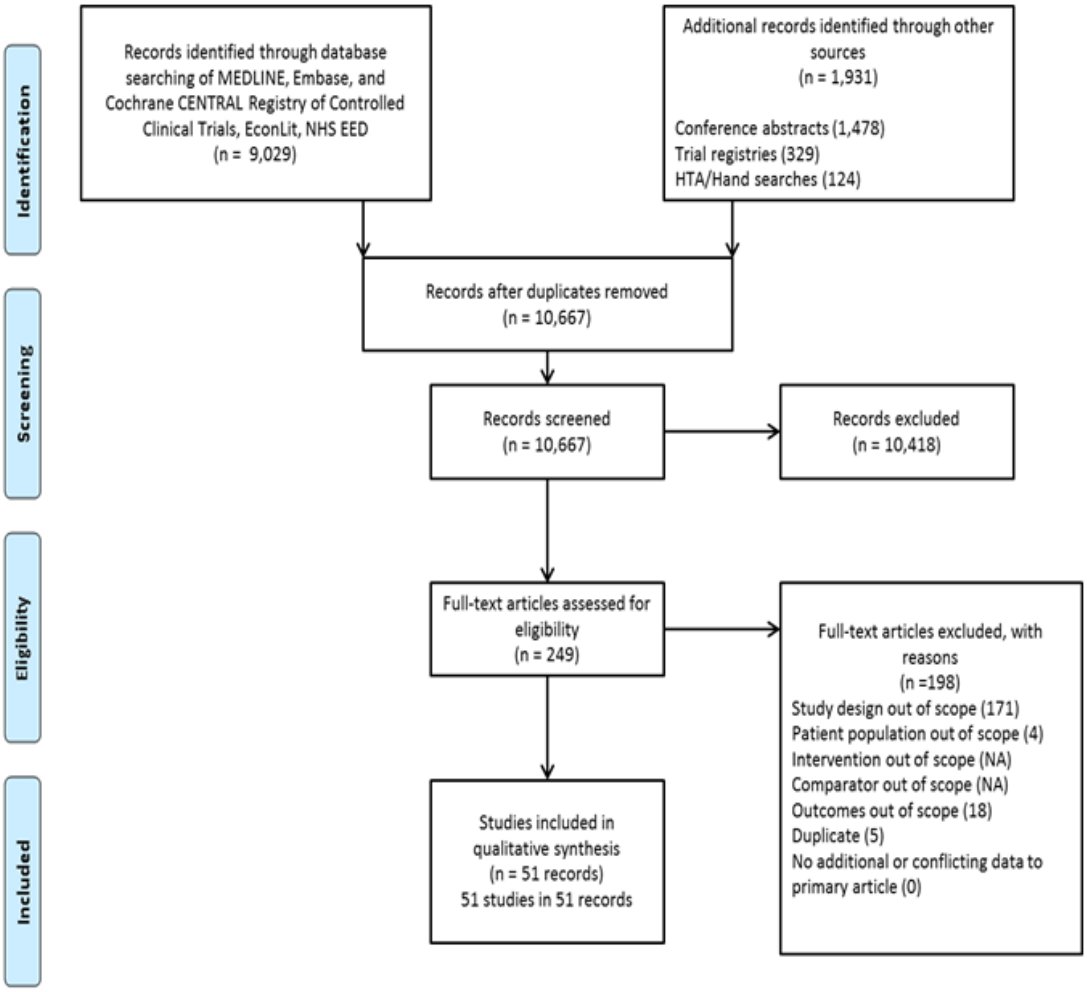
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of mixed cancer populations not reporting results for melanoma separately
Intervention/ Comparators	Not applicable	Not applicable
Outcomes	• Economic model methods • Incremental costs and QALYs • Other efficacy measures with associated costs • Incremental ICER outputs	Not applicable
Study Design	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses • Cost-consequence analyses	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	Not applicable
Date restrictions	Conference proceedings 2013 - present	Not applicable
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UK, United Kingdom		

Study selection results for economic evaluation evidence

The PRISMA flow diagram for the SLR is presented in Figure 5-1 . A total of 10,960 records were retrieved from electronic databases (n=9,029), HTA websites (n=124), clinical trial registry records (n=329) and conference abstracts (n=1,478). Following the removal of

duplicate records, 10,667 titles and abstracts were screened and from these records, a total of 10,418 studies were excluded for various reasons. Subsequently 249 full-text records were screened to determine whether they fulfilled the review inclusion criteria and after detailed review, 51 records reporting data for 51 studies were selected as meeting all of the inclusion criteria and were extracted in full.

Figure 5-1: PRISMA flow diagram for economic evidence



HTA, health technology assessment

Description of Identified studies

Of the 51 studies that were identified and extracted in full, 36 were conducted in patients with stage III to IV melanoma and 15 studies in patients with any stage melanoma.

Of the identified studies, 42 studies reported information on the type of analysis which included cost-utility analysis (n=24), cost-effectiveness analysis (n=12) and both cost-utility and cost-effectiveness studies (n = 6). The model design was reported in 30 studies which included Markov models (n=14), partitioned-survival models (n=7), semi-Markov models (n=3), decision-analytical models (n=3), survival analysis models (n=2), and a budget impact calculator (n=1).The time horizons investigated in the models ranged from 1 to 40 years and

the main cycle length reported ranged from weekly (advanced melanoma) to monthly (any stage melanoma).

Although 51 studies were identified in the SLR only 11 were deemed relevant to the decision problem (Table 5-2) in that they included a relevant comparator as defined in the final scope (T-VEC, ipilimumab, vemurafenib or dabrafenib) and was applicable with regards to the decision making process in a UK HTA setting (in terms of NICE reference case).

Table 5-2: Summary list of published cost-effectiveness studies

First author, year	Model type/ model design	Time horizon and cycle length	Health states	Patient population (average age)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (Cost per QALY gained)
Stage III and IV melanoma								
NICE TA319 2014[2]	CUA / 3-state semi-Markov	ND/1 week	pre-progression Post-progression Death	Stage IIIB–IV, previously untreated MEL (50 years)	IPI DTIC VEM	ND	GBP (ND)	IPI vs. DTIC: £47,899; IPI vs. VEM £28,642
SMC 997/14 2014[118]	CUA / semi-Markov	Time horizon 40 years /1week	ND	Previously untreated advanced (unresectable or metastatic) MEL (ND)	IPI DTIC VEM	ND	GBP IPI: £18,750/3-week cycle; DTIC regimen 1: £75-£83/3-week cycle, regimen 2: £53/3-week cycle; VEM: £5,250/3-week	For BRAF— patients: £31,418
NICE TA268 2012[57]	CUA / Markov	30 years / 1 week	ND	Stage IIIB–IV, previously treated MEL	IPI BSC	ND	GBP (IPI: £92,979; BSC: £12,372)	£60,303; implementing 50% vial sharing reduces ICER to £62,632
NICE TA269 2012[58]	CUA / Markov	5 years / 1 week	ND	Stage IIIC–IV, BRAF V600 mutation MEL (50 years)	VEM DTIC	ND	GBP (VEM: £1,750/pack; DTIC: £63.60/dose)	£75,489

First author, year	Model type/ model design	Time horizon and cycle length	Health states	Patient population (average age)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (Cost per QALY gained)
SMC 792/12 2013[119]	CEA / Survival model	ND / ND	progression-free survival, progressed disease, death	Previously untreated BRAF V600 advanced or metastatic MEL (ND)	VEM DTIC	ND	GBP (VEM: £5,250/3-week cycle; DTIC regimen 1: £72-83/3-week cycle, regimen 2: £53/3-week dose)	£39,617
NICE TA357 2015[59]	CUA / Survival model	5 years / 1 week	progression-free survival, post-progression, death	Advanced (Stage III or IV) MEL (ND)	PEM BSC	ND	GBP (PEM: £1,315/50mg vial)	£42,923
NICE TA321 2014[1]	CUA / Partitioned-survival model	40 year / ND	pre-progression, post-progression, dead	Treatment naive patients with BRAF V600 advanced or metastatic MEL (50 years)	Dabrafenib DTIC VEM	ND	GBP (Dabrafenib: £5,600/28d supply; DTIC: ND; VEM: £1,750/pack)	Dabrafenib vs. DTIC: £49,019; Dabrafenib vs. VEM: £11,028
SMC 1023/15 2015[120]	CUA / Partitioned-survival model	Lifetime / ND	pre-progression, post-progression, dead	Treatment naive patients with BRAF V600 advanced or metastatic MEL (ND)	Dabrafenib DTIC VEM	ND	GBP (Dabrafenib: £36,400/6 mo; DTIC: ND; VEM: £45,500/6 mo)	Dabrafenib vs. DTIC: £49,019; Dabrafenib vs. VEM: £11,028

First author, year	Model type/ model design	Time horizon and cycle length	Health states	Patient population (average age)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (Cost per QALY gained)
Lee 2014[121]	CUA / Partitioned-survival model	35 years / ND	pre-progression, post-progression, dead	BRAF V600 mutation- MEL patients (ND)	Dabrafenib + trametinib DTIC VEM	ND	GBP (ND)	Dabrafenib + trametinib vs. VEM: £50,603; vs. DTIC £49,804
Lee 2012[122]	CUA / Semi-Markov	1 year / ND	pre-progression, post-progression, dead	Previously treated stage IIIB-IV MEL patients (ND)	IPI BSC	ND	USD GBP (ND)	$114,112 £65,303
SMC 779/12 2012[123]	CUA / Markov	Lifetime (40 years) / Cycle length ND	non-progressive disease, progressive disease, terminal disease, death	Previously treated advanced (unresectable or metastatic) MEL patients (ND)	IPI BSC	IPI 1.37 QALY gain BSC ND	GBP (IPI: £18,750/cycle) Lifetime cost £49,602	IPI £36,118 BSC ND

BRAF, B-Raf proto-oncogene, serine/threonine kinase; BSC, best supportive care; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DTIC, dacarbazine; GBP, Great Britain Pound; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; MEL,melanoma; ND, not documented; NICE, National Institute for Health and Care Excellence; PEM, pembrolizumab; QALY, quality-adjusted life year; USD = United States dollar

Quality assessment for each relevant cost-effectiveness study identified

Quality assessments for the extracted studies were conducted using the Drummond and Jefferson instrument (1996)[124]. The Drummond and Jefferson instrument comprises 35 items that assess the comprehensiveness of cost-effectiveness studies. The completed quality assessment for each study is presented in Appendix 1.5.

5.2 De novo analysis

Patient population

In accordance with the anticipated marketing authorisation for T-VEC, the patient population included in the economic evaluation consisted of patients with unresectable regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease (i.e. patients with disease stages IIIB - IVM1a that may or may not have been previously treated).

The clinical evidence for T-VEC was derived from the OPTiM trial and the baseline patient characteristics used in the economic model are presented in Table 5-3.

Table 5-3: Model population base-line characteristics

Characteristic	All lines: stages IIIB-IVM1a	Distribution	Source
Mean age, years	64	Fixed	OPTiM[79]
Proportion male	56%	87.77 to 93.93 (gamma)	
Mean weight, kg	86[a]	74.68 to 83.17 (gamma)	
[a] Dosing calculations for ipilimumab use the mean weight of patients receiving ipilimumab in MDX010-20[72] CA184-0249[93,94]			

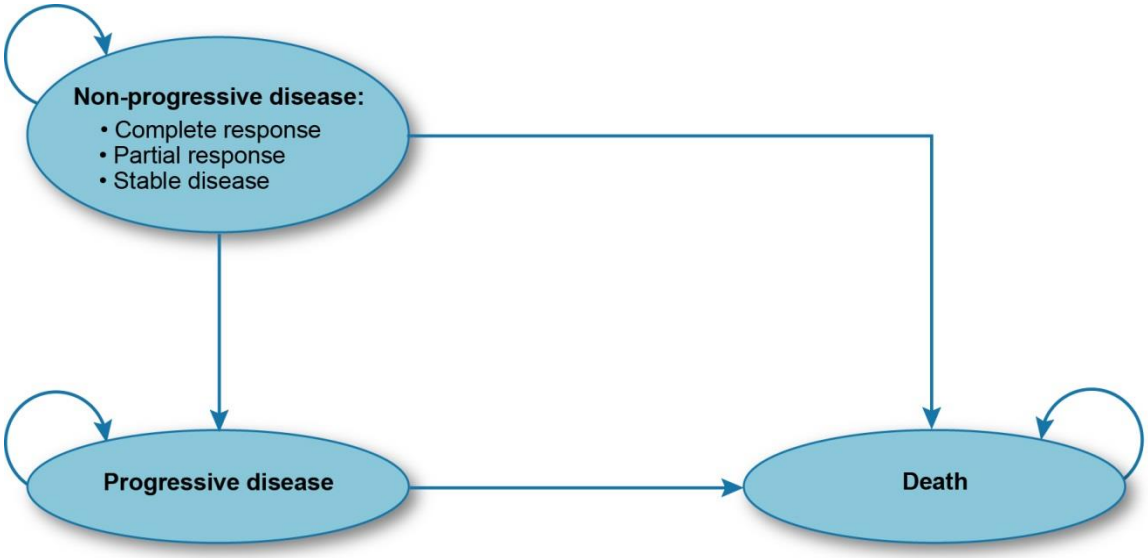
Model structure

A 'partitioned-survival' model was used to predict the long-term costs and health outcomes associated with T-VEC and the primary comparator ipilimumab. Ipilimumab, dabrafenib and vemurafenib are all relevant comparators defined in the decision problem. However for patients with non-visceral metastatic disease (stage IIIB-IVM1a), ipiliumumb is considered to be the primary comparator: Within UK clinical practice, ipilimumab (an immunotherapy like T-VEC) is the likely treatment option for this patient population, since BRAF inhibitors are often reserved for those patients with rapidly progressing disease and high disease burden (NICE guidance (TA319/TA321[1,2] and expert opinion). The structure of the model was designed to appropriately reflect the experiences of patients with advanced stage IIIB - IV M1a melanoma and consisted of three mutually exclusive health states:

- Non-progressive disease, comprising of complete response (CR), partial response (PR), and stable disease (SD).
- Progressive disease (PD).
- Death (absorbing state).

Figure 5-2 illustrates the core model structure with possible transitions between the different health states indicated by arrows.

Figure 5-2: Economic model structure



Patients enter the model in the non-progressive disease state and receive treatment with either T-VEC or ipilimumab. Transition to another health state is dependent on response to treatment, in which patients may respond to treatment (CR or PR), progress to a worse health state (PD or death), or remain stable (i.e., there is neither response nor disease progression).

Upon disease progression, patients in both treatment arms of the model were assumed to receive best supportive care (BSC). BSC is defined as non-curative health care received by patients in the period between disease progression and administration of palliative care. Patients who died were assumed to have received palliative care for up to 3 months before death, in line with previous NICE appraisals; patients who died also were assumed to have received terminal care prior to death.

The clinical definition of each health state was based on the OPTiM trial and described in Table 5-4.

Table 5-4: Health State Definitions

Health state		Definition	Reference
Non-progressive disease	CR	Disappearance of all clinical evidence of tumour	OPTiM[79]
	PR	≥ 50% reduction from baseline in the sum of the surface area of all measurable tumours	
	SD	Neither sufficient overall tumour shrinkage to qualify for response (CR or PR) nor sufficient tumour increase to qualify for PD	
Progressive disease	PD	> 25% increase in the sum of the surface areas of all measurable tumours, or a single lesion increase of > 25% (over the smallest measurement achieved for the single lesion), or the appearance of a new lesion	
Death		Death from any cause	-
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease			

PD is assumed to be a determinant of quality of life and healthcare resource utilisation. Health-related quality of life (HRQoL) is expected to improve for patients who respond to treatment and conversely, HRQoL is expected to deteriorate for patients whose disease progresses.

The model enables the differences in the quality of life, decrements in utility associated with adverse events and disease management costs to be captured in each health state by considering five phases of disease management, independent of active treatment:

- On-treatment pre-progression (routine treatment): the health care received while in the non-PD state.
- On-treatment disease progression: the health care received when switching to best supportive care (BSC) because of disease progression BSC: the non-curative health care received in the period between disease progression and administration of palliative care.
- Palliative care: the health care received up to 3 months before death.
- Terminal care: the health care received immediately prior to death.

Features of the de novo analysis

The model perspective is in line with the NICE reference case and reflects that of the National Health Service and Personal Social Services. All costs and effects were discounted by 3.5% annuallyand a lifetime time horizon of 30 years was used. A cycle length of 1 week consistent with previous cost-effectiveness models in advanced melanoma[1,2,58] was assumed and a half-cycle correction was applied. The key model features of the *de novo* analysis are outlined in Table 5-5.

Table 5-5: Features of de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (up to 30 years after initiation of treatment)	A 30-year life time horizon was judged to be most appropriate to capture the life time differences in costs and outcomes associated with metastatic melanoma[2,57]
Cycle length	1 week	A 1-week cycle length was considered sufficient to capture transitions between the different health states to quantify all meaningful differences in technologies compared and is consistent with previous melanoma models that had have been validated by clinical experts[1,2,58]
Half-cycle correction	Yes	NICE Reference Case[125]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference Case[125]
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case[125]
Perspective (NHS/PSS)	NHS and PSS	NICE Reference Case[125]

NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-year.

Intervention technology and comparators

T-VEC dosing and treatment duration

As described in Section 4.3:

- Patients in the OPTiM trial remained on treatment for at least 6 months even in the event of disease progression (unless intolerability or alternate therapy was required based on assessment of the patient's clinical status)[79]. This is reflected in the anticipated marketing authorisation and is also reflected in the estimated of T-VEC dose and treatment duration.
- In the OPTiM trial, an accelerated dosing schedule could be invoked, in which the frequency of injections into any progressing lesion(s) could be increased to once per week for 4 weeks and up to three sets of four accelerated injections could be given (as long as after each set of four accelerated injections, clinically relevant disease progression did not occur and there was still residual tumour to inject[79]. Accelerated dosing is not recommended in the anticipated license for T-VEC[4]; (Appendix 1.1). Patients who received accelerated doses in the trial had poor survival outcomes compared to patients who did not receive accelerated dosing. In routine clinical practice, it is anticipated that clinicians would not increase dosing frequency of T-VEC especially given that alternatives treatment options are available. Consequently the base-case analysis excludes accelerated doses (Section 5.5).
- In the OPTiM trial patients who had successfully completed treatment were eligible to enter into an extension study if they did not have disease progression during the OPTiM study or had a CR but developed new lesions within 12 months[80]. In the extension study patients continued with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity. A small proportion of patients (9.8%) on the T-VEC arm entered the extension phase. 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 (September 2014). This provides complete information on T-VEC dosing and reduces the uncertainty regarding treatment duration (Section 5.5).

Ipilimumab

The licensed dosing regimen for ipilimumab is 3 mg/kg administered intravenously over a 90-minute period and given every three weeks for a total of four doses[47]. For the model, the dosing for ipilimumab was based on a previous ipilimumab NICE appraisal (TA319) and was (conservatively) lower than that stated in the SPC. Further details are described in Section 5.5.

Discontinuation rules

No clinical discontinuation rules were implemented. The model assumes that patients are treated with T-VEC or the relevant comparators in accordance with their current marketing authorisations.

5.3 Clinical parameters and variables

Describe how the clinical data were incorporated in the model

Clinical data from the studies identified for the assessment of comparative effectiveness using the Korn methodology was used to populate key parameters in the model, namely, the proportion of patients under the key health states, OS and PFS, as well as the proportion of patients experiencing AEs and the proportion of patients under the different health states for the assignment of health state utility values. The studies included were:

- OPTiM: pivotal phase III trial of T-VEC versus GM-CSF for the treatment of unresected stage IIIB/C and IV melanoma[79].
- CA184-024 pivotal phase III trial in previously untreated advanced melanoma patients that investigates the efficacy of ipilimumab 10mg/kg in addition to DTIC therapy[88,89].
- MDX010-020 pivotal phase III trial in chemotherapy-naïve advanced melanoma patients that report the efficacy of ipilimumab 3mg/kg monotherapy[72,92-94].

It should be underscored that given the unfeasibility of carrying out a NMA and the issues around reliability of results with the alternative methodology (Korn adjustment) to assess comparative effectiveness between T-VEC and the BRAF-inhibitors, the cost-effectiveness section focuses on the key comparator ipilimumab only. It is noteworthy that NICE, in previous discussions around melanoma appraisals, accepted the clinical supposition that ipilimumab is comparable to vemurafenib (TA319) and dabrafenib is comparable to vemurafenib (TA321)[1,2].

For the cost-effectiveness assessment of T-VEC compared to ipilimumab, the final data cut (September 2014) for T-VEC was used and the published clinical trial data for ipilimumab (CA182-024 and MDX010-020) was pooled together and used. As discussed in Section 4.11, the most mature published Kaplan Meier data from the ipilimumab pivotal trials were digitised and 'adjusted' using the modified Korn algorithm and the two-step Korn algorithm to generate survival curves that approximate the expected survival in a population similar to that of the OPTiM trial. Specifically, the Korn adjustment was applied to the OS and PFS Kaplan-Meier data to account for the different baseline characteristics observed across the ipilimumab trials and the OPTiM trial.

In order to capture the survival distributions observed in the trials and extrapolate them beyond the trial periods, the following approaches were used:

Overall Survival

A piecewise curve fitting approach was used where a single cut-point was applied to the Kaplan Meier OS curve to enable a large proportion of the observed data to be captured. Regression models were applied after the cut-point to estimate long-term survival up to the end of observed data of the respective clinical trials, at which it is assumed there was no more treatment effect. From the end of the trial to 10 years, the mortality rates from the AJCC[22] and UK life table[126] were used to combine the likelihood of death from melanoma and all-cause mortality. From 10 years onwards UK life table data are used. Similar approaches have been used in the recent NICE Technology Appraisals of ipilimumab (TA319)[2] and dabrafenib (TA321)[1] and have been acknowledged as a suitable method to model survival in this disease area.

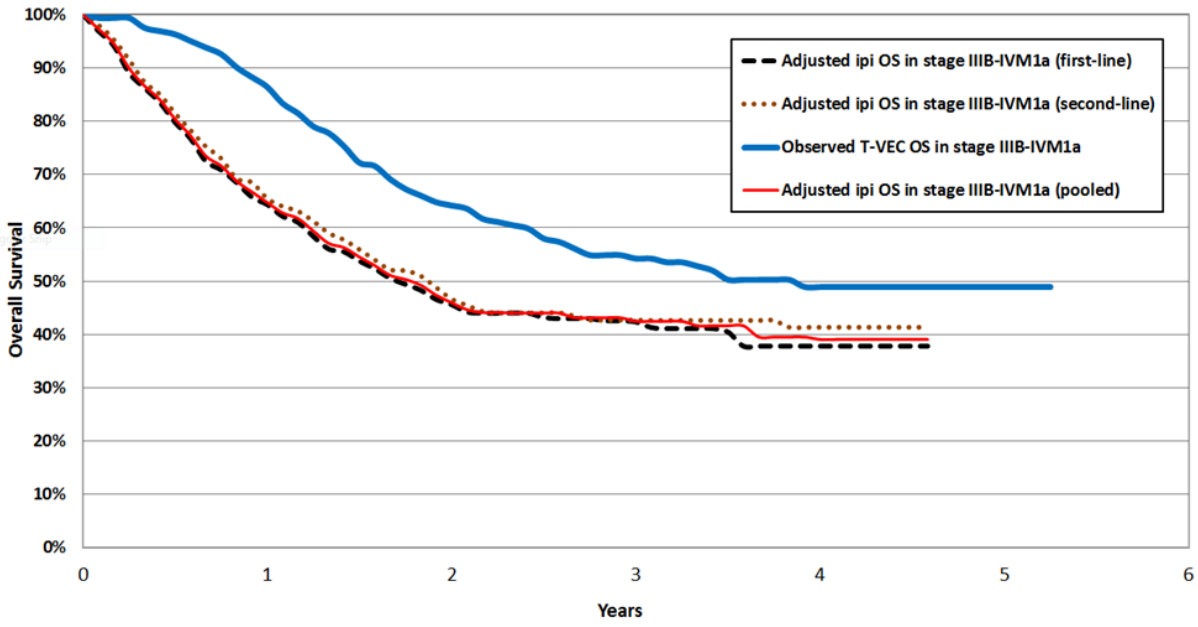
Progression free survival:

Regression models were applied to the PFS Kaplan Meier curve to project survival across all periods. Attempts were made to fit regression models pre- and post-cut point where the hazards significantly change. However, given that the detected cut points were quite late in follow-up (90-162 weeks) and resulted in few patients (9-10 patients) and even fewer events (1-4 events) to fit parametric curves to post-cut point, a piece-wise approach was deemed inappropriate. For long-term PFS, post-Kaplan Meier hazards for T-VEC were conservatively set to the same as the hazards for the comparator.

Modelling OS for T-VEC and ipilimumab – 3 part curve fit

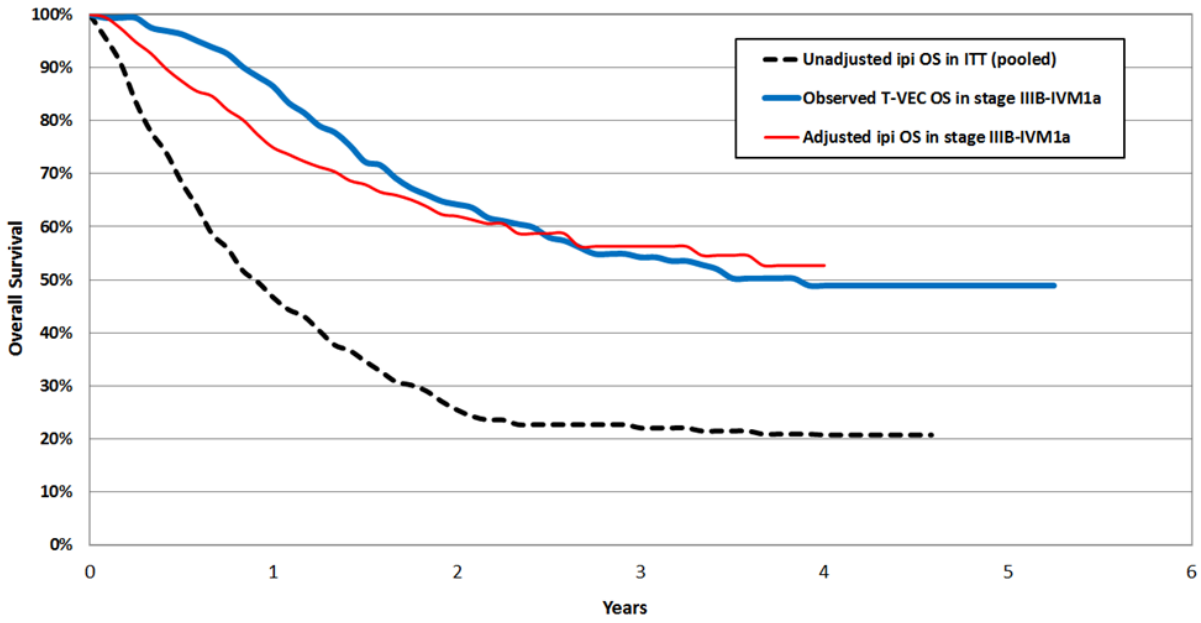
The modified Korn adjustment and two-step Korn adjustment demonstrate that there is a plausible chance that T-VEC provides an improvement in survival over ipilimumab in its anticipated licensed population (non-visceral metastatic disease) and, at worse, is no less effective. Figure 5-3 and Figure 5-4 presents the adjusted Kaplan Meier OS curve for ipilimumab in patients with stage IIIB-IVM1a disease using the modified Korn and two-step Korn methods respectively.

Figure 5-3: Modified Korn adjusted Kaplan Meier OS curve for ipilimumab in patients with stage IIIB-IVM1a disease



ipi, ipilimumab; OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-4: Two-step Korn adjusted Kaplan Meier OS curve for ipilimumab in patients with stage IIIB-IVM1a disease



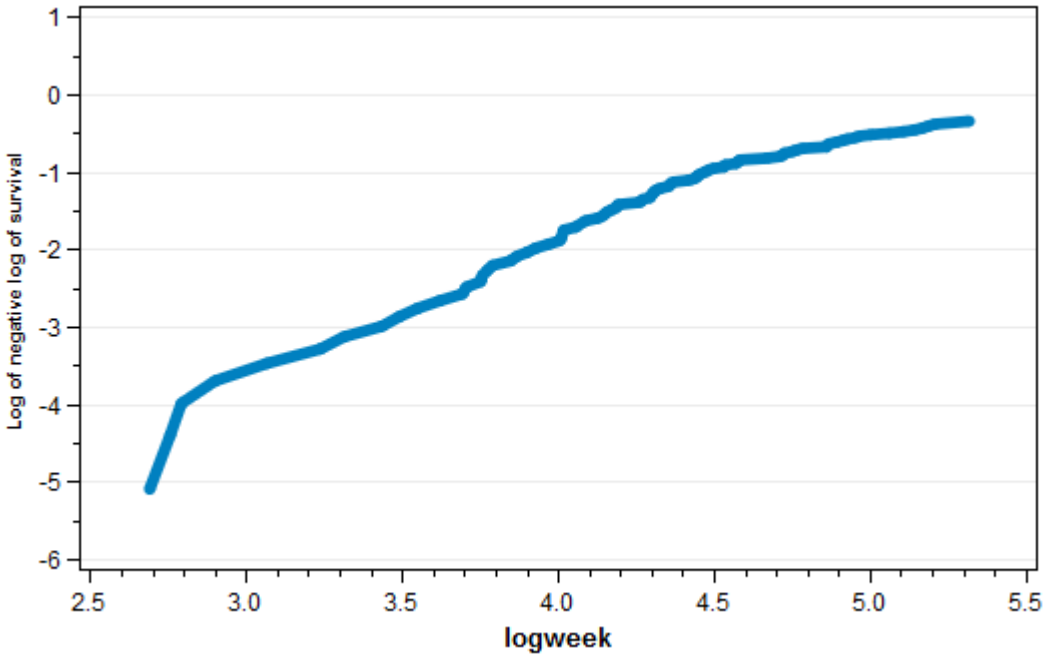
ipi, ipilimumab; ITT, intent-to-treat; OS, overall survival; T-VEC, talimogene laherparepvec

Following the modified Korn adjustment and two-step Korn adjustment methods, OS for T-VEC and ipilimumab was modelled using a 3 part curve fit. The NICE Decision Support Unit model selection algorithm was used in order to select the most appropriate extrapolation model for modelling OS[127]. The standard parametric models which included the exponential, Weibull, Gompertz, generalised gamma, loglogistic and log-normal were considered and the fit of alternative models was assessed by considering internal and external validity and the plausibility of the extrapolated results. Alternative methods to the standard parametric curve fit to extrapolate survival beyond the trial period were explored in a sensitivity analyses. The long-term extrapolation of survival was based on observational disease-specific data and general population life table data.

First part of the 3-part curve fit

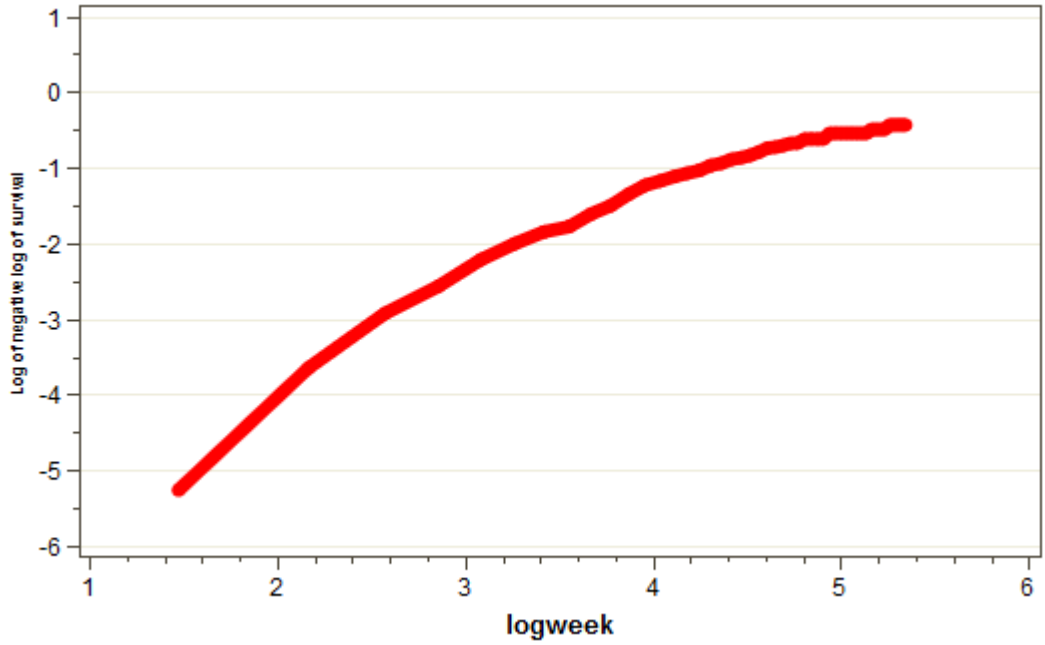
The cut point in the 3 part curve fit was determined by estimating structural changes to the Kaplan Meier curve using Chow tests[128,129]. The structural changes to the slope of the Kaplan Meier curves were tested and the time point with the most pronounced change to the slope of the Kaplan Meier curve was selected as the cut point. The log cumulative hazard curves for T-VEC (Figure 5-5) and ipilimumab (adjusted OS using modified Korn model; Figure 5-6) show that the hazard is not constant over time.

Figure 5-5: Log cumulative hazard plot for OS: T-VEC



OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-6: Log cumulative hazard plot for OS: Ipilimumab



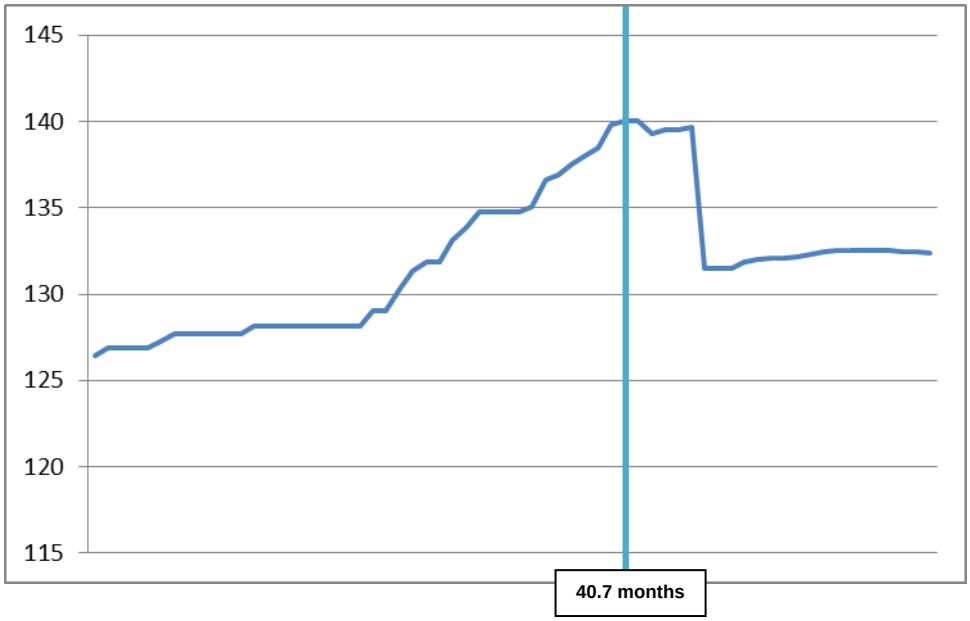
OS, overall survival

The results of the Chow tests are provided in Table 5-6, Figure 5-7 , Figure 5-8 and Figure 5-9 and show that for T-VEC, the Kaplan Meier curve was used until 40.7 months and for ipilimumab, the Kaplan Meier curve was used until 29.7 months

Table 5-6: Cut-points for T-VEC and Ipilimumab OS curves

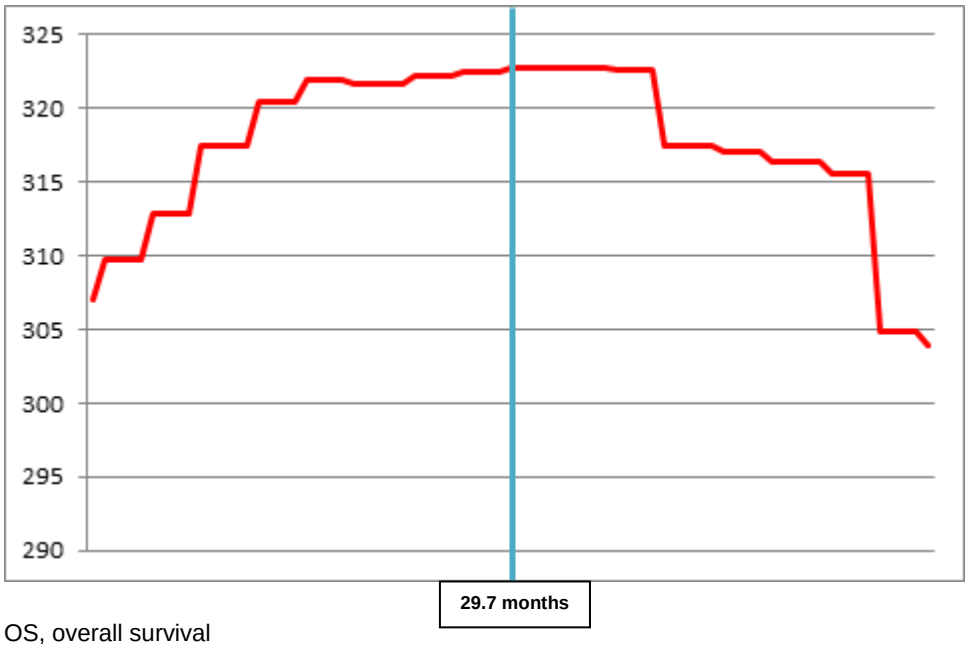
Intervention	Cut point (months)
T-VEC	**40.7**
Ipilimumab	**29.7**
OS, overall survival; T-VEC, talimogene laherparepvec	

Figure 5-7: Results from the Chow Test for T-VEC OS Curve



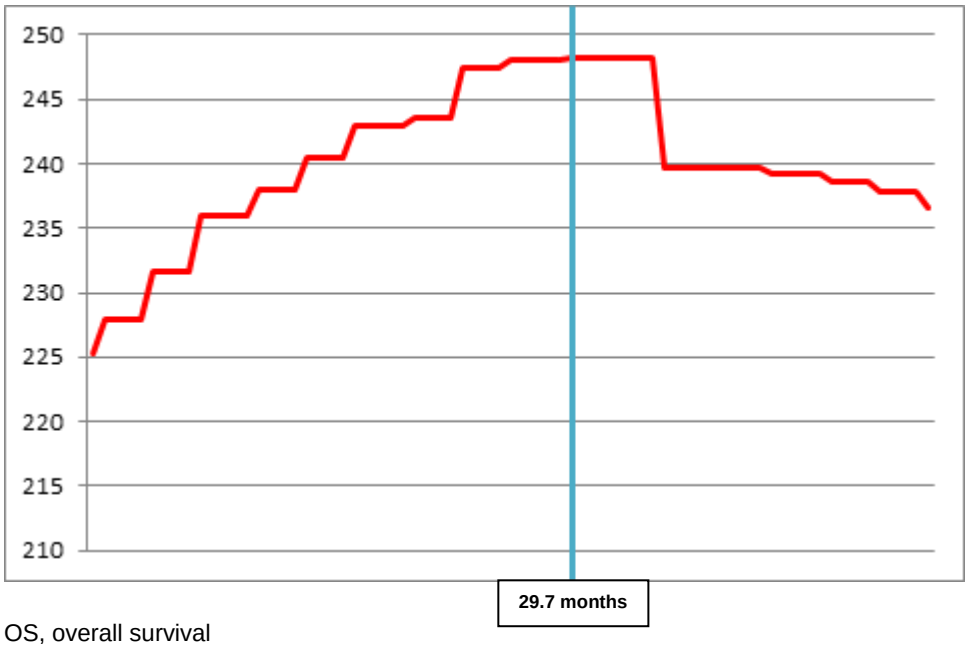
OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-8: Results from the Chow Test for ipilimumab OS Curve based on the modified Korn adjustment



OS, overall survival

Figure 5-9: Results from the Chow Test for ipilimumab OS Curve based on two-step Korn adjustment



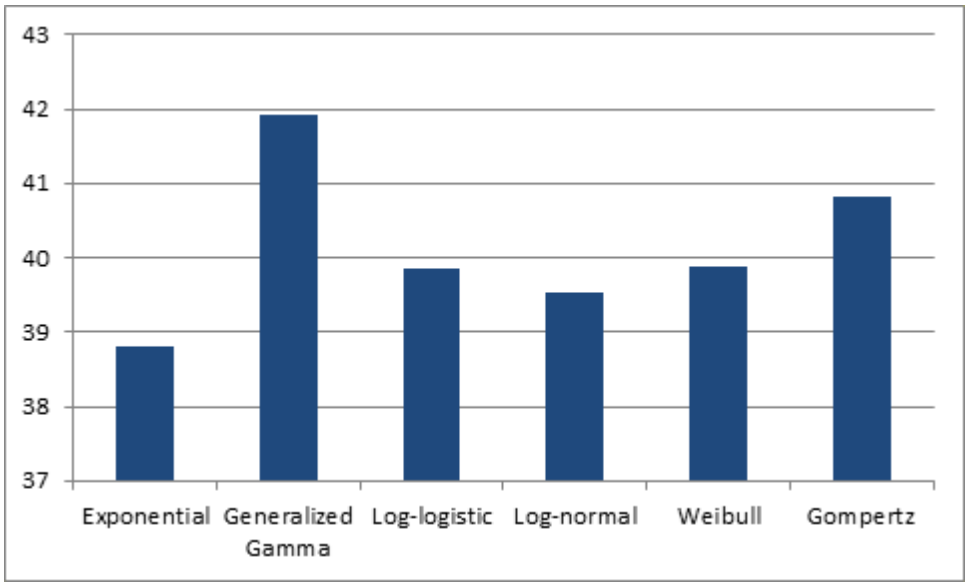
OS, overall survival

Second part of the 3-part curve fit

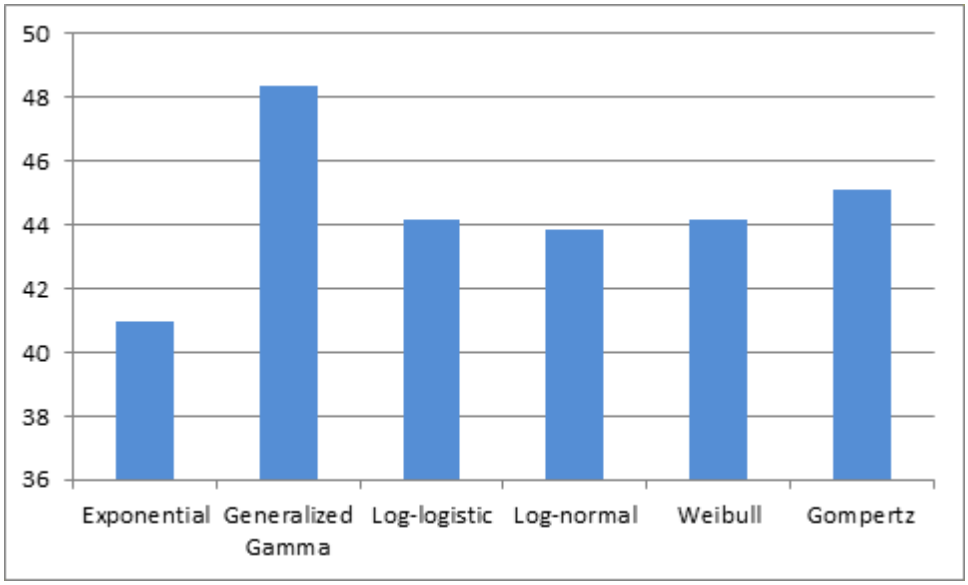
A fitted parametric curve was used from the start of the cut point to the end of the observed data from the trials (62 months and 55 months for T-VEC and ipilimumab respectively). The curve fits for the parametric curves portion were based upon goodness of fit tests, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Figure 5-10, Figure 5-11 and Figure 5-12). Based on visual inspection as well as goodness of fit tests, an exponential curve fit was used for both T-VEC and ipilimumab and the impact of using various curve fits is explored under sensitivity analysis (Section 5.8).

Figure 5-10: AIC and BIC goodness of fit statistics for OS curve fits for T-VEC

AIC



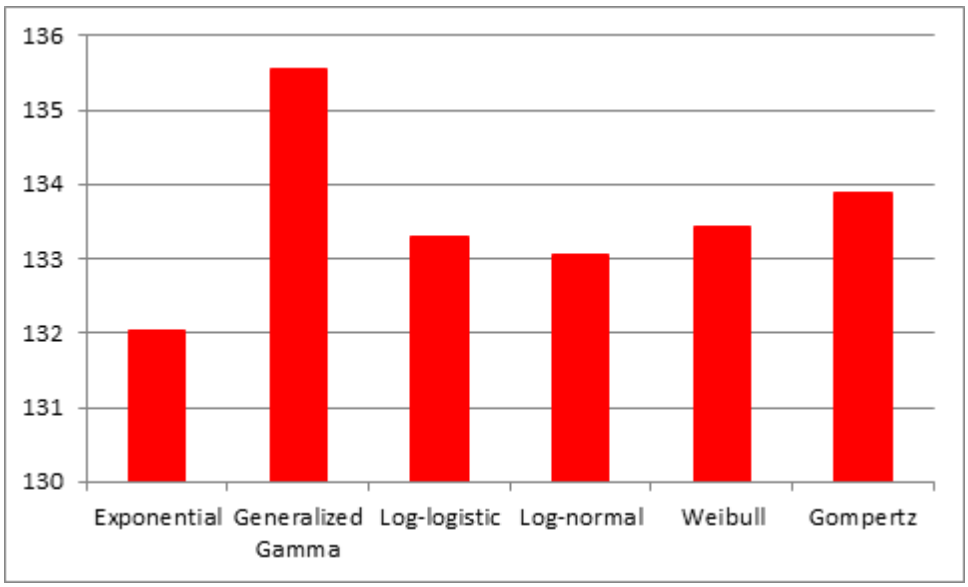
BIC



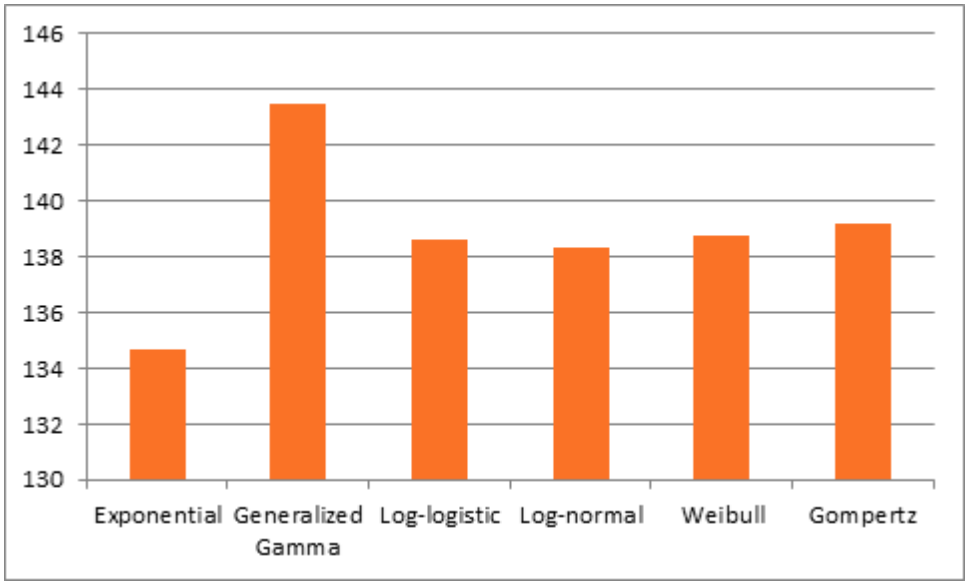
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-11: AIC and BIC goodness of fit statistics for OS curve fits for Ipilimumab based on modified Korn

AIC



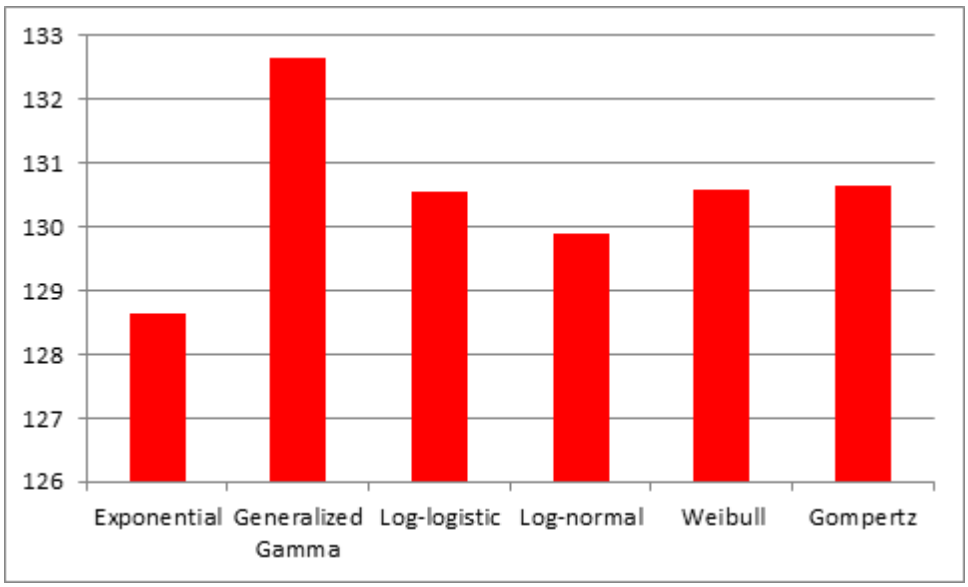
BIC



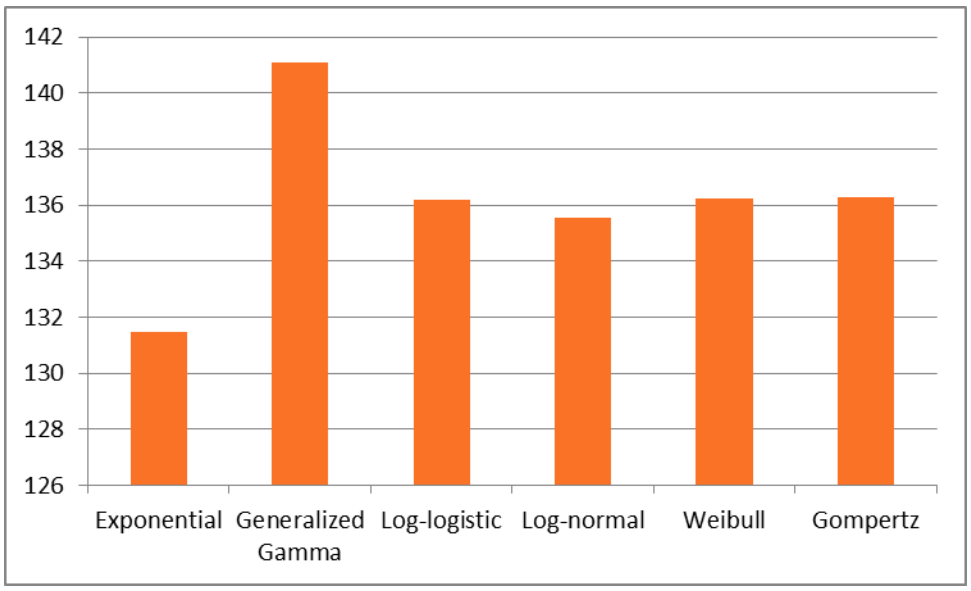
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-12: AIC and BIC goodness of fit statistics for OS curve fits for Ipilimumab based on two-step Korn

AIC



BIC



AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Third part of the 3-part curve fit

By the end of the trials, no further treatment effect is assumed. The long-term extrapolation of survival beyond that observed in the trials (62 months and 55 months for T-VEC and ipilimumab respectively) was based on observational disease-specific data from the AJCC[22] and mortality data from life tables published by the Office of National Statistics[126]. Balch 2009 registry data were selected for the base case analysis as it provided the most up to date data.

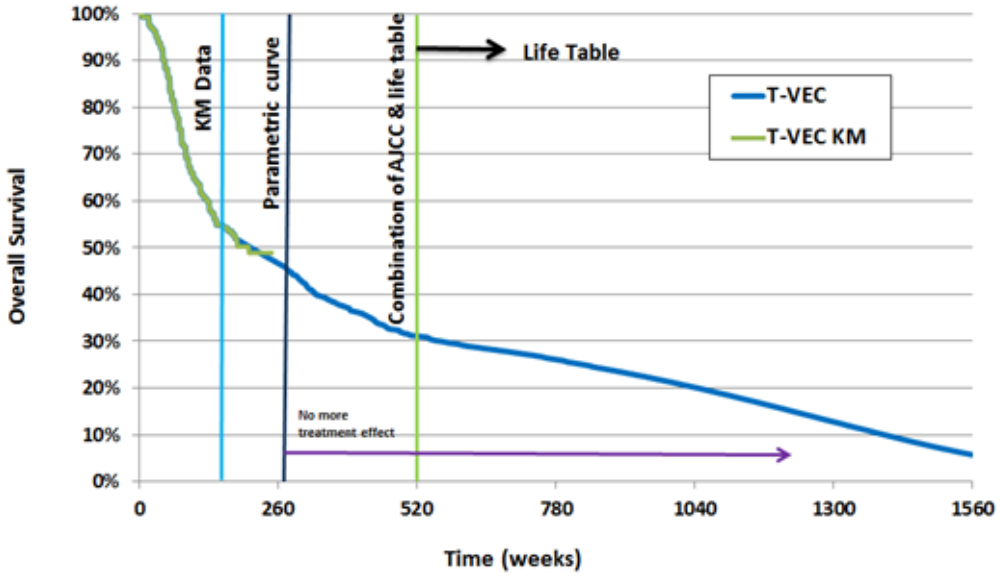
A weighted average AJCC survival curve was constructed using disease stage; i.e., AJCC by disease stage was weighted to match the distribution of disease stage at baseline in the T-VEC arm of the OPTiM trial. Mortality risk was also included from the start of the AJCC data, using data from life tables published by the Office of National Statistics. These data were also weighted according to the age and sex distribution in the T-VEC and ipilimumab trials, to ensure consistency in the age-and sex-adjusted long-term mortality. The data were used to estimate survival for the remainder of the time horizon (AJCC and life table data up to 10 years, then on the life table data alone from 10 years onwards as there are no remaining melanoma-based hazards).

The base case OS curve is described in Table 5-7 below and the OS curves estimated using the 3-part curve fit approach are displayed in Figure 5-13 to Figure 5-15.

Table 5-7: T-VEC and ipilimumab base case OS curve using 3 part curve fits

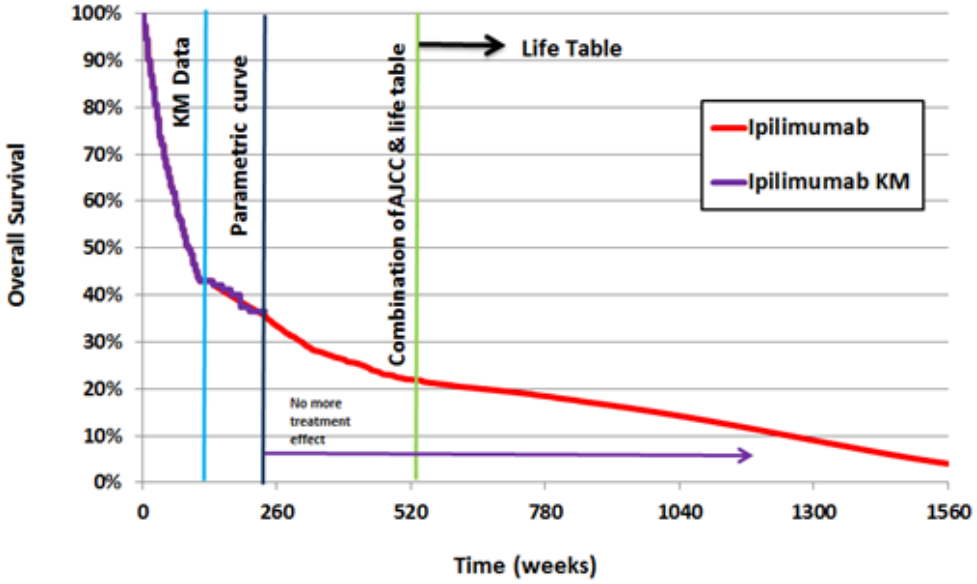
Curve part	Duration	Curve fit and parameters	Source
T-VEC			
KM data	Cycles 0-177	N/A	OPTiM[79]
Parametric curve	Cycles 178-269	Exponential Intercept: 5.1359 Scale: 1.0000	Curve fitted to survival of patients alive at 177 weeks
Registry data hazards and life table, then life table alone	Cycles 270+	N/A	Balch et al 2009[22] Life table[126]
Ipilimumab based on modified Korn			
KM data	Cycles 0-129	N/A	CA184-024[88,89], MDX 10-20[72,92,93] clinical trials, NICE TA319[2]
Parametric curve	Cycles 130-239	Exponential Intercept: 4.91090 Scale: 1.0000	Curve fitted to survival of patients alive at 130 weeks
Registry data hazards and life table, then life table alone	Cycles 240+	N/A	Balch et al 2009[22] Life Table[126]
Ipilimumab based two-step Korn			
KM data	Cycles 0-129	N/A	CA184-024[88,89], MDX 10-20[72,92,93] clinical trials, NICE TA319[2]
Parametric curve	Cycles 130-239	Exponential Intercept: 4.75610 Scale: 1.0000	Curve fitted to survival of patients alive at 130 weeks
Registry data hazards and life table, then life table alone	Cycles 240+	N/A	Balch et al 2009[22] Life Table[126]
KM, Kaplan Meier; N/A not applicable; OS, overall survival; T-VEC, talimogene laherparepvec			

Figure 5-13: T-VEC OS 3 part curve fit



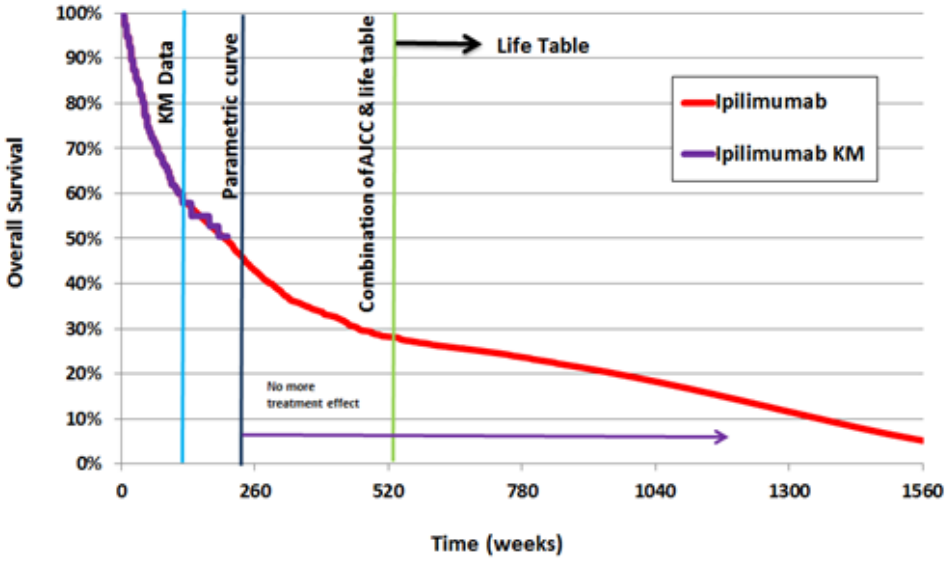
AJCC; American Joint Committee on Cancer; KM, Kaplan-Meier; OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-14: Ipilimumab OS (based on modified Korn adjustment) 3 part curve fit



AJCC; American Joint Committee on Cancer; KM, Kaplan-Meier; OS, overall survival

Figure 5-15: Ipilimumab OS (based on two-step Korn adjustment) 3 part curve fit



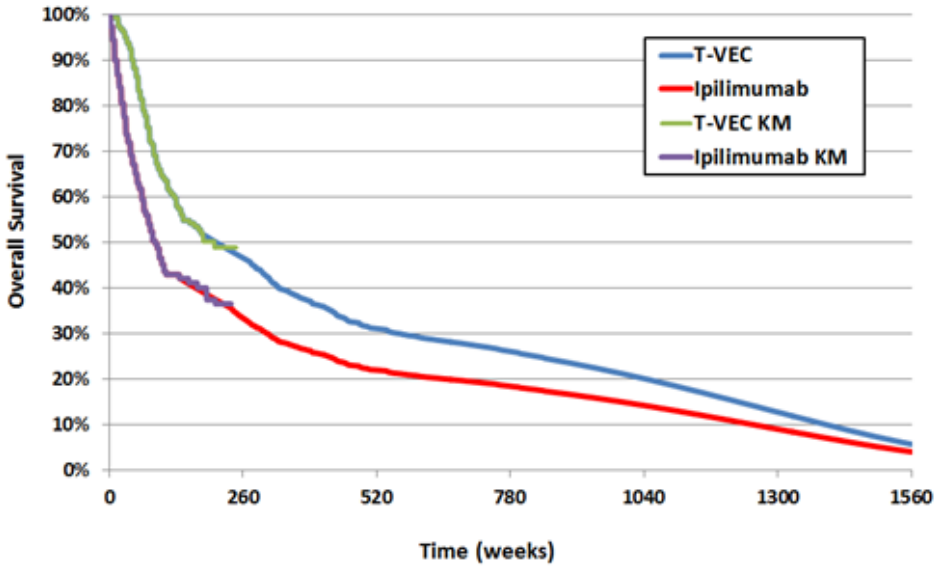
AJCC; American Joint Committee on Cancer; KM, Kaplan-Meier; OS, overall survival

The final estimated overall survival predictions for T-VEC and ipilimumab using the 3-part curve fit and the modified Korn adjustment and the two-step Korn are presented in Figure 5-16 and Figure 5-17. As discussed in Section 4.11, there is no published data for ipilimumab in the anticipated T-VEC licensed population. Although T-VEC has robust data in the non-visceral metastatic (stage IIIB – IVM1a) patient population, the dearth of data for the comparators presents genuine uncertainty around the critical clinical issue of the treatment effect of the comparators in non-visceral metastatic disease.

The modified Korn adjustment adjusts for the baseline prognostic variables and assumes that there is no interaction with treatment for patients with non-visceral metastatic disease except that beyond disease stage prognosis. This may be deemed to be the most favourable scenario of the OS gain of T-VEC versus ipilimumab with 1.76 life years (6.66 years and 4.90 years for T-VEC and ipilimumab respectively (Figure 5-16).

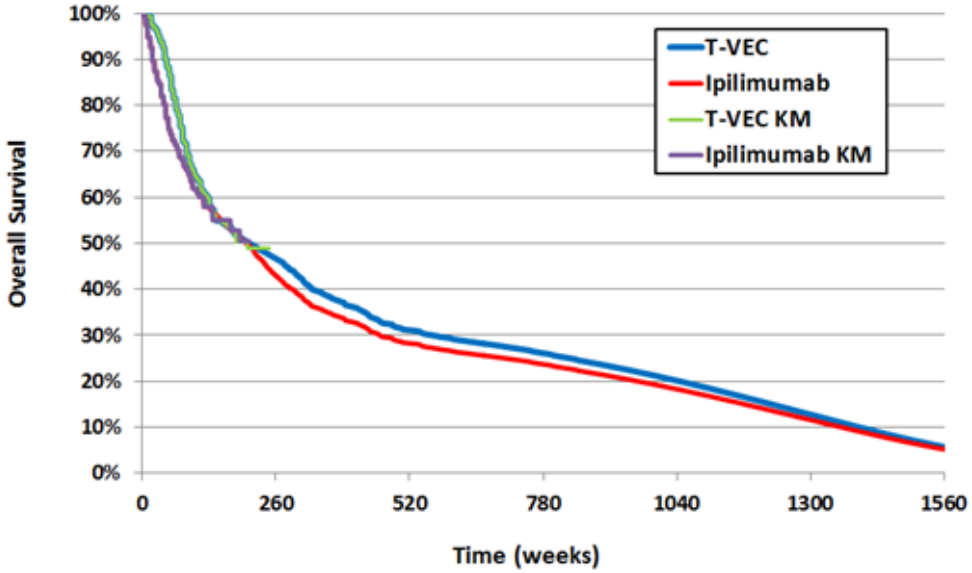
The two-step Korn adjustment, in contrast, not only assumes the presence of an interaction effect but also assigns the best possible magnitude of this effect to ipilimumab. Consequently, the resulting mean OS gain for T-VEC of 0.5 life years (6.66 years and 4.90 years for T-VEC and ipilimumab respectively, may be deemed to be the worse-case scenario for T-VEC (Figure 5-17).

Figure 5-16: Comparative OS for T-VEC and ipilimumab (based on the modified Korn adjustment)



KM, Kaplan-Meier; OS, overall survival; T-VEC, talimogene laherparepvec

Figure 5-17: Comparative OS for T-VEC and ipilimumab (based on the two-step Korn adjustment)



KM, Kaplan-Meier; OS, overall survival; T-VEC, talimogene laherparepvec

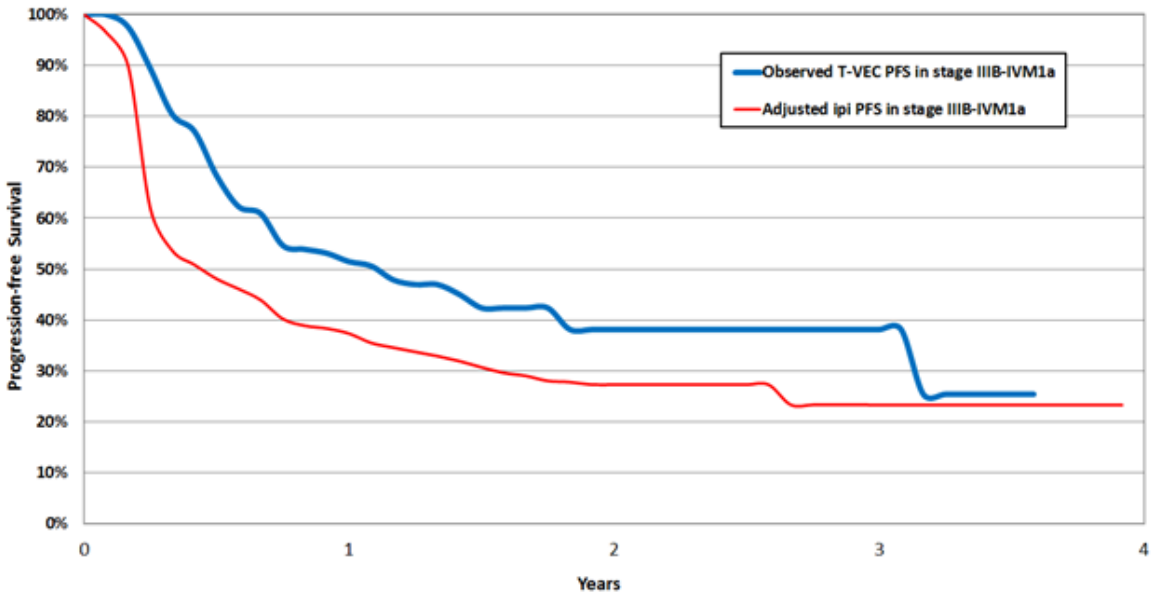
Modelling progression free survival for T-VEC and Ipilimumab

To model and extrapolate PFS, similar to the case for OS, attempts were made to fit regressions pre- and post-cut point where hazards significantly change. However, for PFS, the detected cut points were quite late in follow-up (162 weeks for T-VEC and 90 and 98 weeks for ipilimumab based on the Korn OS adjustments) and resulted in few patients (9 to 10 patients) and even fewer events (1 to 4 events) to fit parametric curves post cut point. It is also noteworthy that the post-cut point regressions did not converge due to the issue of very few patients and events as described above. Therefore, a regression was fitted to project

PFS across all periods rather than using the curve fit approach based on cut points. For long-term PFS, post-Kaplan-Meier hazards for T-VEC were conservatively set to the same hazards as the comparator.

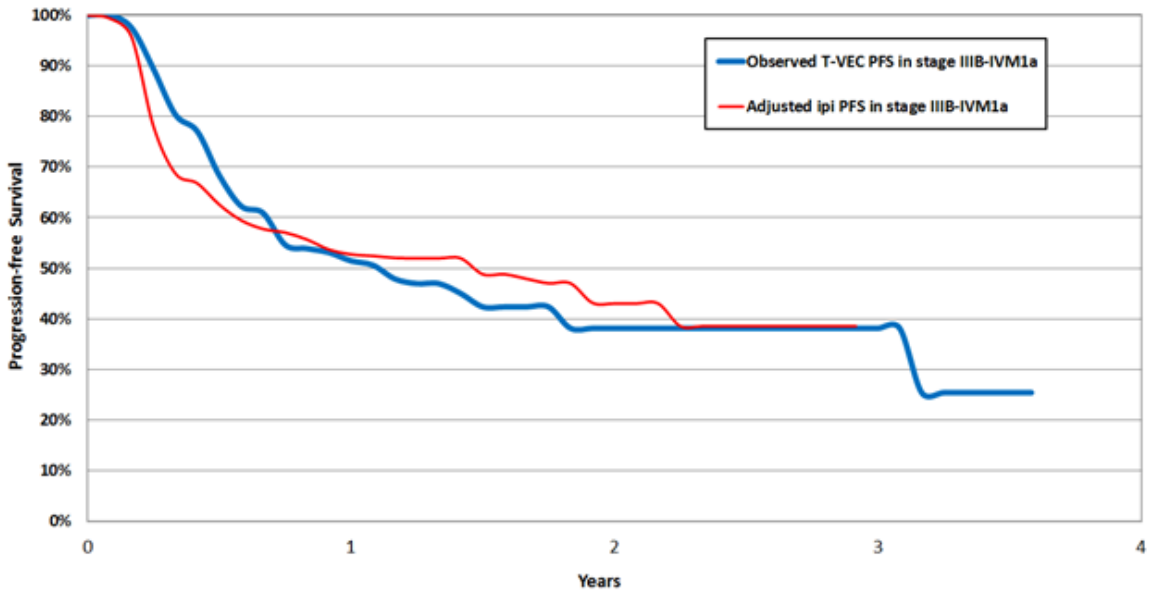
Figure 5-18 and Figure 5-19 below present the adjusted Kaplan Meier PFS, based on the modified Korn adjustment and the two-step Korn adjustment for ipilimumab in patients with stage IIIB-IVM1a disease.

Figure 5-18: Modified Korn adjusted Kaplan Meier PFS curve for ipilimumab in patients with stage IIIB-IVM1a disease



Ipi, ipilimumab; PFS, progression-free survival; T-VEC, talimogene laherparepvec

Figure 5-19: Two-step Korn adjusted Kaplan Meier PFS curve for ipilimumab in patients with stage IIIB-IVM1a disease

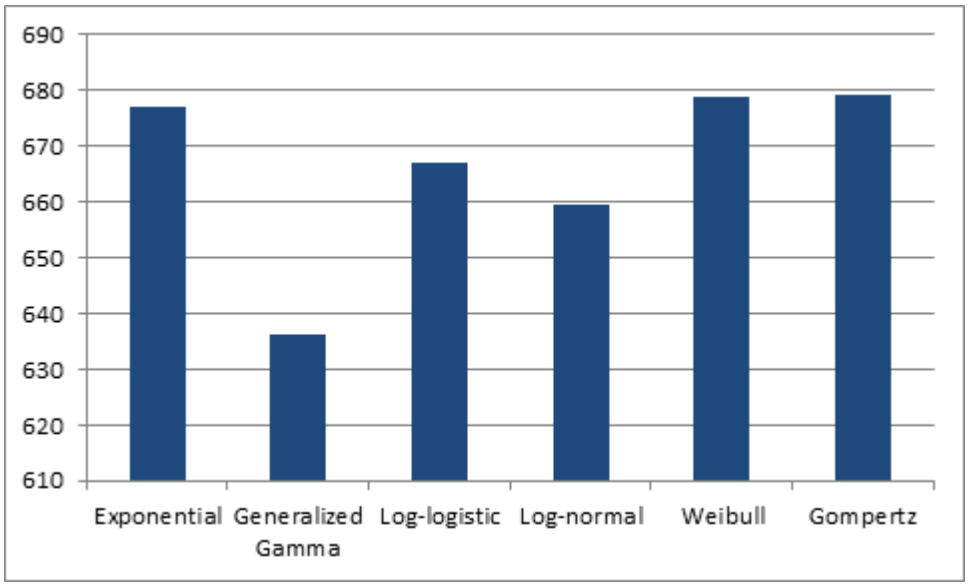


PFS, progression-free survival; T-VEC, talimogene laherparepvec

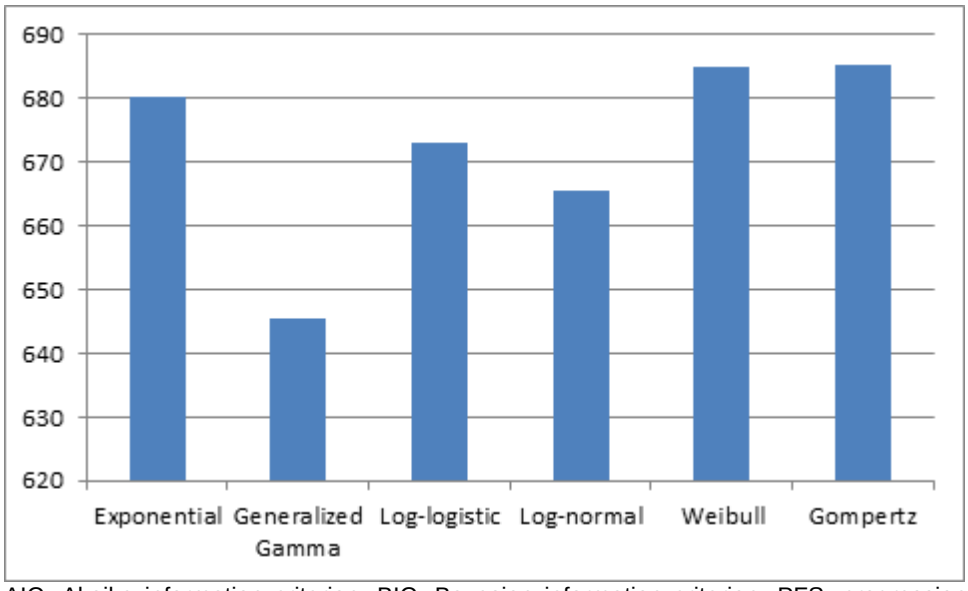
A fitted parametric curve was used to extrapolate PFS. The curve fits for the parametric curves were based upon goodness of fit tests, AIC and BIC (Figure 5-20 and Figure 5-21). Based on visual inspection as well as goodness of fit tests, a generalised gamma curve was used for both T-VEC and ipilimumab and the impact of using various curve fits is explored under sensitivity analysis.

Figure 5-20: AIC and BIC goodness of fit statistics for PFS curve fits for T-VEC

AIC



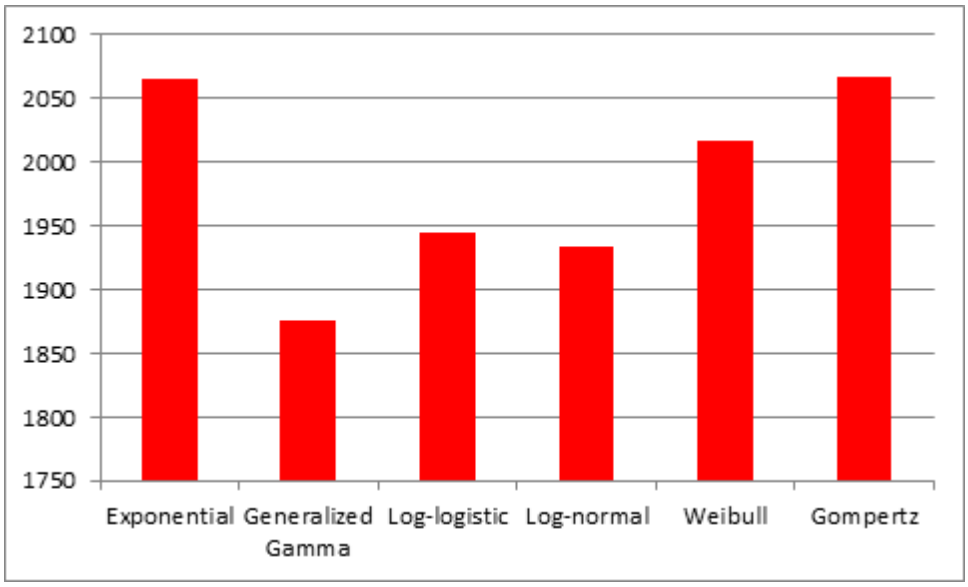
BIC



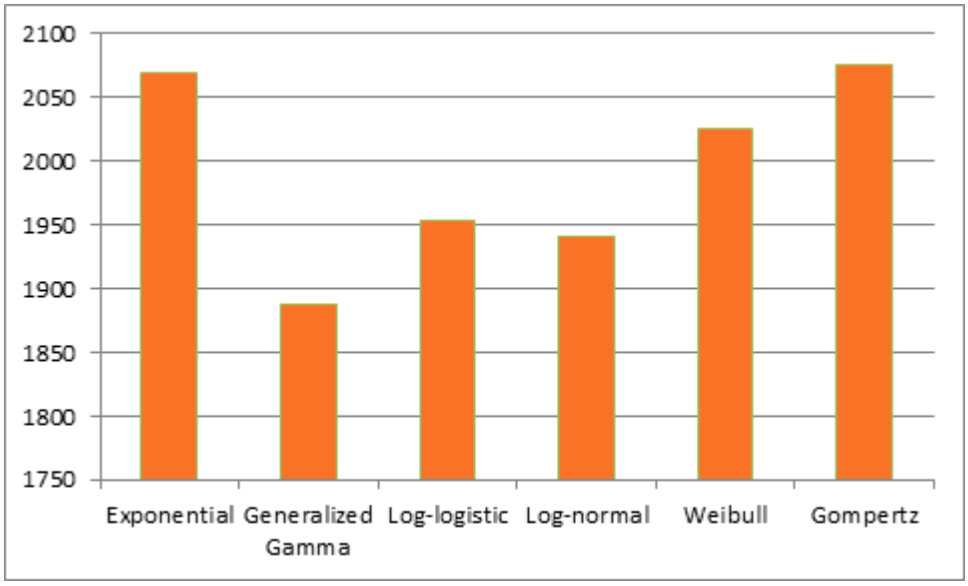
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; T-VEC, talimogene laherparepvec

Figure 5-21: AIC and BIC goodness of fit statistics for PFS curve fits for ipilimumab based on modified Korn adjustment

AIC



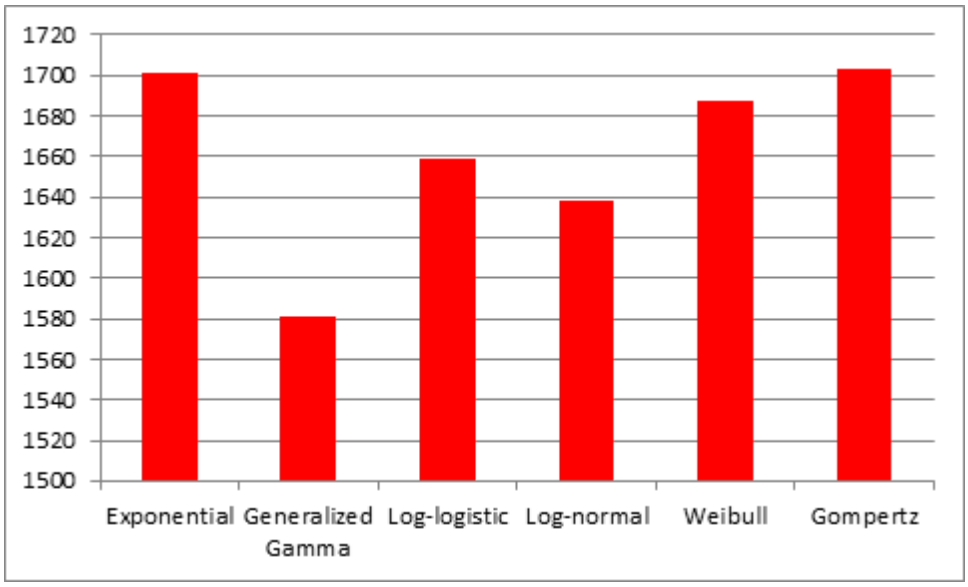
BIC



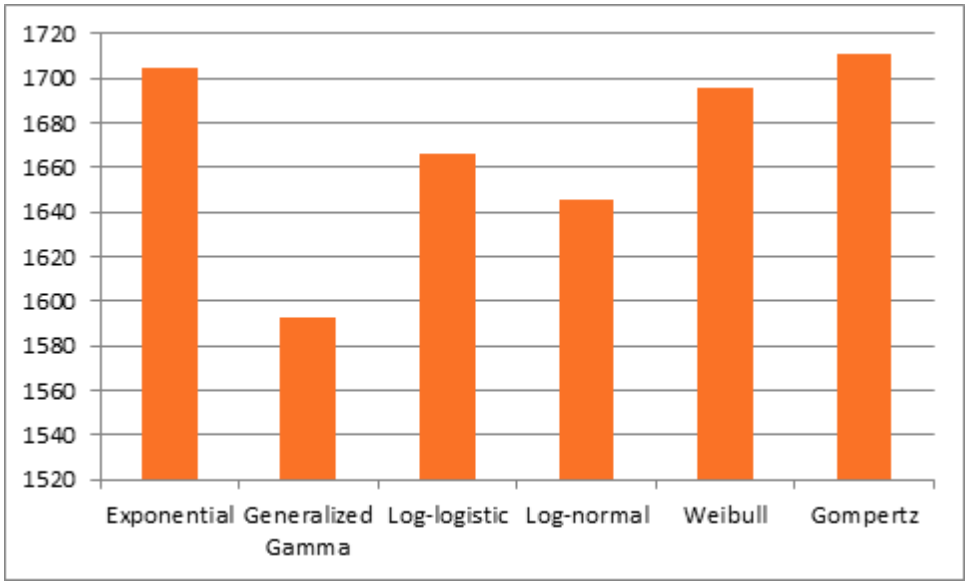
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival

Figure 5-22: AIC and BIC goodness of fit statistics for PFS curve fits for ipilimumab based on two-step Korn adjustment

AIC



BIC



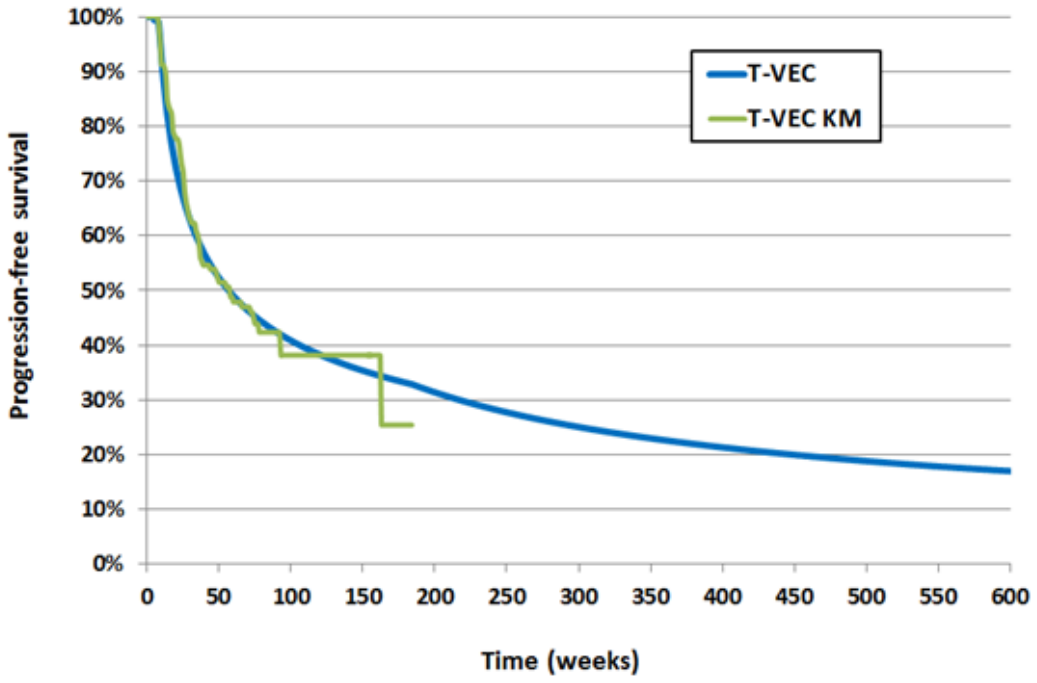
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival

The base case curve is described in Table 5-8 below and the estimated PFS curves are displayed in Figure 5-23 to Figure 5-25.

Table 5-8: T-VEC and ipilimumab base case PFS curve using regression

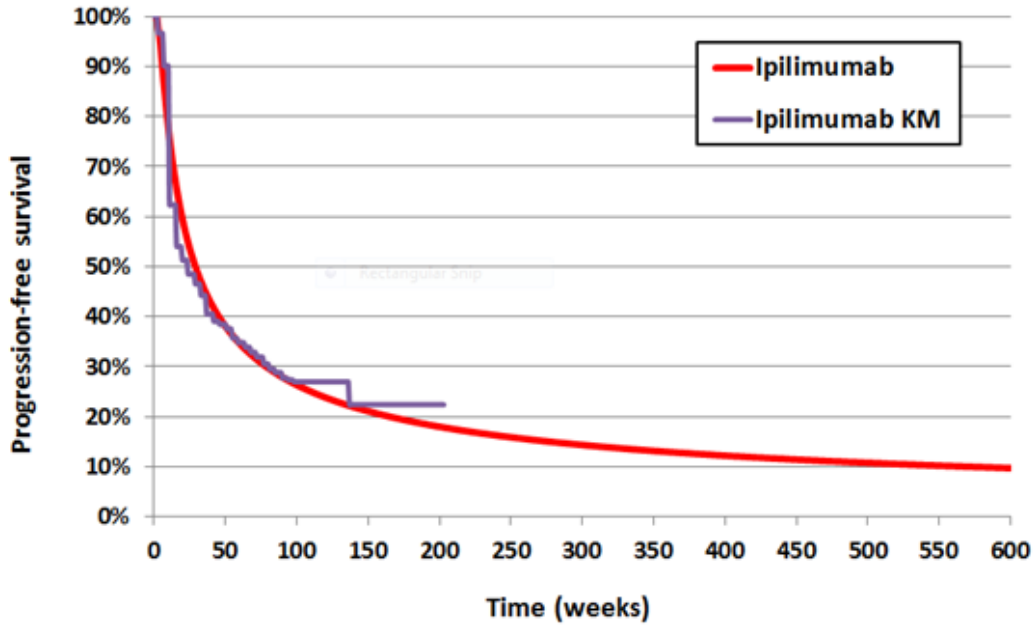
Curve part	Duration	Curve fit and parameters	Source
T-VEC			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 0.85010 Scale: 0.46000 Shape: -6.10950	Curve fitted to PFS of all patients
Ipilimumab (Based on Modified Korn adjustment)			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 1.20460 Scale: 1.26720 Shape: -1.39870	Curve fitted to PFS of all patients
Ipilimumab (Based on two-step Korn adjustment)			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 1.44460 Scale: 1.27410 Shape: -2.05300	Curve fitted to PFS of all patients
Abbreviations: PFS, progression free survival; T-VEC, talimogene laherparepvec			

Figure 5-23: One curve fit for T-VEC PFS



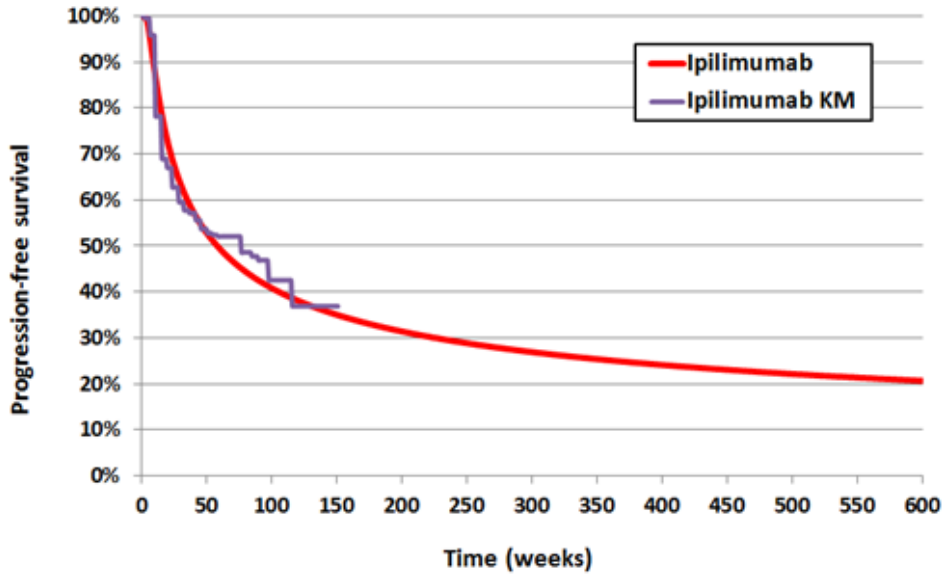
KM, Kaplan Meier; PFS, progression free survival; T-VEC, talimogene laherparepvec

Figure 5-24: One curve fit for ipilimumab PFS (based on modified Korn adjustment)



KM, Kaplan Meier; PFS, progression free survival

Figure 5-25: One curve fit for ipilimumab PFS (based on two-step Korn adjustment)



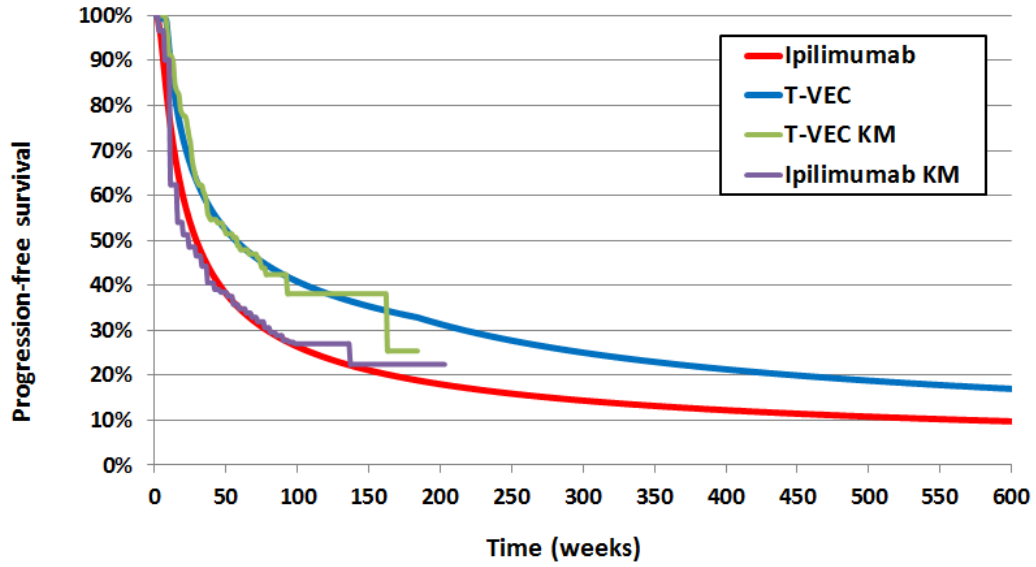
KM, Kaplan Meier; PFS, progression free survival

The final estimated PFS predictions for T-VEC and ipilimumab using the modified Korn adjustment is shown in Figure 5-26 below. Similarly, Figure 5-27 shows the same based on the two-step Korn adjustment.

As discussed previously, the paucity of data for ipilimumab in patients with non-visceral metastatic disease, presents genuine uncertainty around the critical clinical issue of the treatment effect in non-visceral metastatic disease. The modified Korn adjustment adjusts for the baseline prognostic variables and assumes that there is no interaction with treatment for patients with non-visceral metastatic disease except that beyond disease stage prognosis.

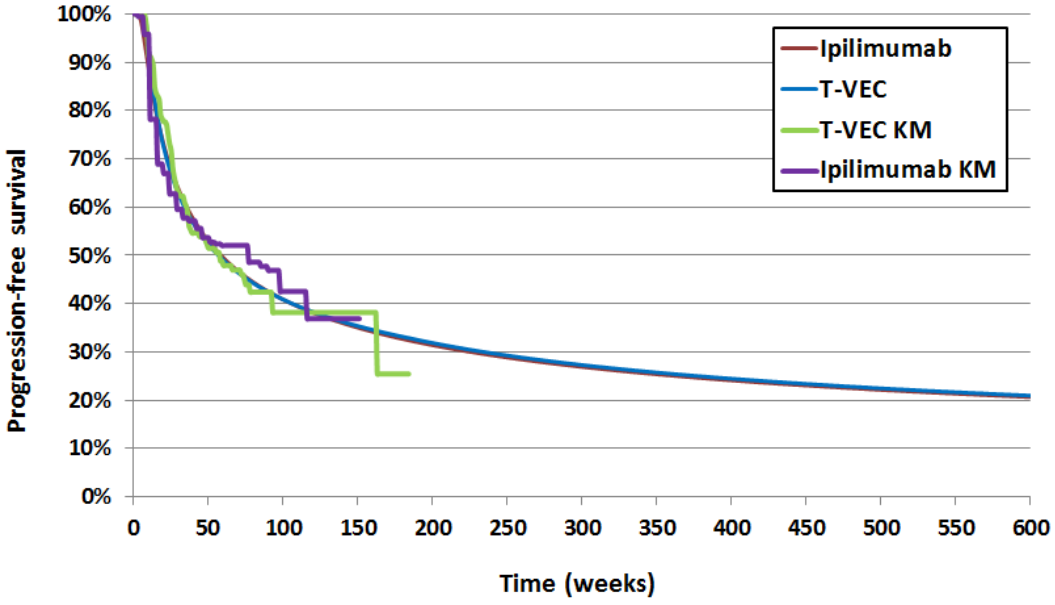
This may be deemed to be the most favourable scenario of the PFS gain of T-VEC versus ipilimumab (Figure 5-26) of 1.55 years (4.22 years and 2.67 years for T-VEC and ipilimumab respectively,. The two-step Korn adjustment (Figure 5-27), in contrast not only assumes the presence of an interaction effect but also assigns the best possible magnitude of this effect to ipilimumab. Consequently, the resulting mean PFS gain for T-VEC of 0.08 years (4.69 years and 4.62 years for T-VEC and ipilimumab respectively) may be deemed to be the worse-case scenario for T-VEC.

Figure 5-26: Comparative PFS for T-VEC and ipilimumab (based on Modified Korn adjustment)



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

Figure 5-27: Comparative PFS for T-VEC and ipilimumab (based on two-step Korn adjustment)



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

Calculation of transition probabilities from the clinical data

Transition probabilities are not applicable given the structure of the model, however as described in Section 5.3, the model was developed by fitting survival curves to the observed trial data for OS and PFS, and the proportion of patients in each health state was determined as follows:

- Non-progressive/pre-progressive disease health state was equal to whichever was lower of the OS or PFS curve in each cycle. This approach resolved any conflicts in instances where the OS curve estimated a lower probability of survival than the PFS curve.
- Progressive disease health state was equal to the difference between the OS and PFS curves in each cycle
- Dead health was equal to the complement of the OS curve in each cycle

Evidence that (transition) probabilities may change over time

A detailed description of the extrapolation methods was previously provided above.

Input from clinical experts

The clinical parameters used in the economic model were derived from the available evidence; three clinical experts in the field of melanoma and a health economist were consulted to discuss the clinical plausibility of the indirect comparison of T-VEC and the relevant comparators, the approach to survival modelling and the plausibility of the survival estimates generated from the clinical data.

The selection of the clinical experts was based upon their availability and all had experience of T-VEC and the comparators defined in the decision problem either in a clinical trial or through routine clinical practice. The clinicians practiced in three different geographical locations across the UK and received an honorarium for their review which was conducted via individual telephone interviews.

There was general agreement that the efficacy of T-VEC versus GM-CSF in the anticipated license population was clinically meaningful and significant. There was also acknowledgement of the challenges of performing an indirect comparison (given broken networks and heterogeneity of patient populations) to estimate the survival gain between T-VEC versus ipilimumab and consequently the Korn methodology was deemed to be an appropriate method given these challenges.

5.4 Measurement and valuation of health effects

Melanoma can have a significant impact on the HRQoL of patients, with many patients facing physical, emotional and psychological challenges. Additionally, many treatments for advanced melanoma are associated with significant toxicity resulting in symptoms such as diarrhoea, nausea, stomatitis, hair loss and flu-like syndrome that can also have an impact on a patient's quality of life[130].

Although patients with metastatic disease may have a high level of functioning at diagnosis, rapid progression of disease leads to a decline in almost all of the major physical and social functional domains[33]. Long term survival due to clinical improvement is expected to result in an increase in utility or the utility remaining the same; however for patients who do not

become long-term survivors, the quality of life has been shown to decrease with a large reduction the quality of life in the month prior to death[131,132].

Health-related quality-of-life data from clinical trials

Summary of clinical data

As described in Section 4.8, quality of life was assessed in OPTiM using the FACT-BRM and patients were required to complete the questionnaire prior to any treatment-related study procedures (including administration of investigational product) on day 1 of each treatment cycle and at the end of trial visit.

Baseline questionnaires were completed by 95.7% of patients in the T-VEC arm and 82.6% in the GM-CSF arm, with completion rates in subsequent cycles lower in both arms of the trial. Additionally, a more rapid decline in the questionnaire completion rates was observed for patients in the GM-CSF arm compared to those in the T-VEC arm which was most likely related to the differences in the rate of treatment discontinuation, disease progression and death in the GM-CSF arm (Section 4.8; Table 4-19).

Analysis of the FACT-BRM showed that more patients treated with T-VEC than those treated with GM-CSF had an improvement in all 11 subscales of the questionnaire (Figure 4-9) and a statistically significant difference in favour of T-VEC was observed in 6 of the measures (Emotional Well-Being, Functional Well-Being, Social/Family Well-Being, overall QoL, pain, and ability to work).

Amgen time trade-off study

A separate Amgen sponsored time-trade off (TTO) utility study was conducted to elicit the preferences of members of the UK general public for health states associated with advanced melanoma (Appendix 1.7). The health states assessed in the study were consistent with the patient outcomes in the OPTiM trial and the health states in the economic model (Section 5.2). Only AEs with an incidence of at least 2% in patients receiving treatment with various therapies for advanced melanoma (including T-VEC, ipilimumab, vemurafenib and dabrafenib) were included in the study, and the health state descriptions were validated by six healthcare professionals (three oncologists and three oncology nurses) experienced in the treatment of advanced melanoma.

Participants (n=300) were recruited from the general public in three different geographical locations across the UK and were asked to rate their own health using the EQ-5D-3L and Visual Analogue Scale (VAS), and also rate the health state descriptions using the VAS and TTO. The results from the study are detailed in Appendix 1.7 and show that the VAS scores and the mean TTO utility values for each health state trended in the direction expected for health state severity and as expected the mean utility values for PD, CR, and PR were the highest, and PD and BSC had the lowest utility values.

Stable disease was used as the anchoring state for the calculation of increments or decrements in utility, and further details on disutilities are provided in Section 5.4. The results from the TTO study have been explored in the sensitivity analysis, and further details on the identification of utility values for the cost-effectiveness model are described in Section 5.4, with the values implemented in the model presented in Section 5.6.

Consistency with NICE reference case

The FACT-BRM is not a preference based measure of HRQoL and does not conform to the NICE reference case.

Given that the trial based HRQoL data is inconsistent with the NICE reference case, HRQoL data from the literature has been used in the economic model which is consistent with previous NICE appraisals in metastatic melanoma[2,57,58].

Mapping

Mapping was not undertaken and the utility values utilised in the base-case modelling were based on a recent NICE TA in melanoma (TA321)[1]. The model also included disutilities from adverse events based on a preference elicitation study by Amgen (Section 5.4).

Health-related quality-of-life studies

Systematic searches for relevant HRQoL

A SLR was conducted in September 2015 to identify published HRQoL studies for advanced (unresectable or metastatic) melanoma.

Search strategy

The search included peer-reviewed journal articles, HTA documents, and data from relevant conference proceedings. Full details are provided in Appendix 1.2. The following databases were searched for relevant studies:

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.
- PsycInfo (OvidSP): 1806 to September Week 1 2015

Supplementary searches were undertaken for the following trials registers from inception to March 2015:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- EU Clinical Trials Register (EUCTR) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- PharmaNet.Bund (http://www.pharmnet-bund.de/static/de/index.html)
- National Institutes of Health (NIH) Clinical Trial Registry (CTR)
- Australian New Zealand Clinical Trials Registry (ANZCTR) (http://www.anzctr.org.au/TrialSearch.aspx)

Further supplementary searches were undertaken in relevant conference abstracts from 2013 to present:

- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(http://www.ispor.org/)

- European Association of Dermato Oncology (EADO) (http://www.eado.org/)
- European Cancer Congress (ECC) (http://www.esmo.org/Conferences/European-Cancer-Congress-2015)
- Society of Melanoma Research (SMR) (http://www.societymelanomaresearch.org/)
- Perspectives in Melanoma (PIM) (http://imedex.com/perspectives-melanoma-conference/)

Additionally, a reference list review of reports identified through a manual search of HTA websites was also under taken for the:

- UK:
  - NICE (www.nice.org.uk)
  - AWMSG (http://www.awmsg.org/app/search?execution=e1s1)
  - SMC (http://www.scottishmedicines.org.uk/Home)
- Canada
  - CADTH (http://www.cadth.ca)

Study selection

Study inclusion was not limited by language, HTA reviews were restricted to the UK (England, Scotland, Wales) and Canada, and the publication date for conference proceedings was limited to 2013. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 5-9.

Table 5-9: Study inclusion and exclusion criteria

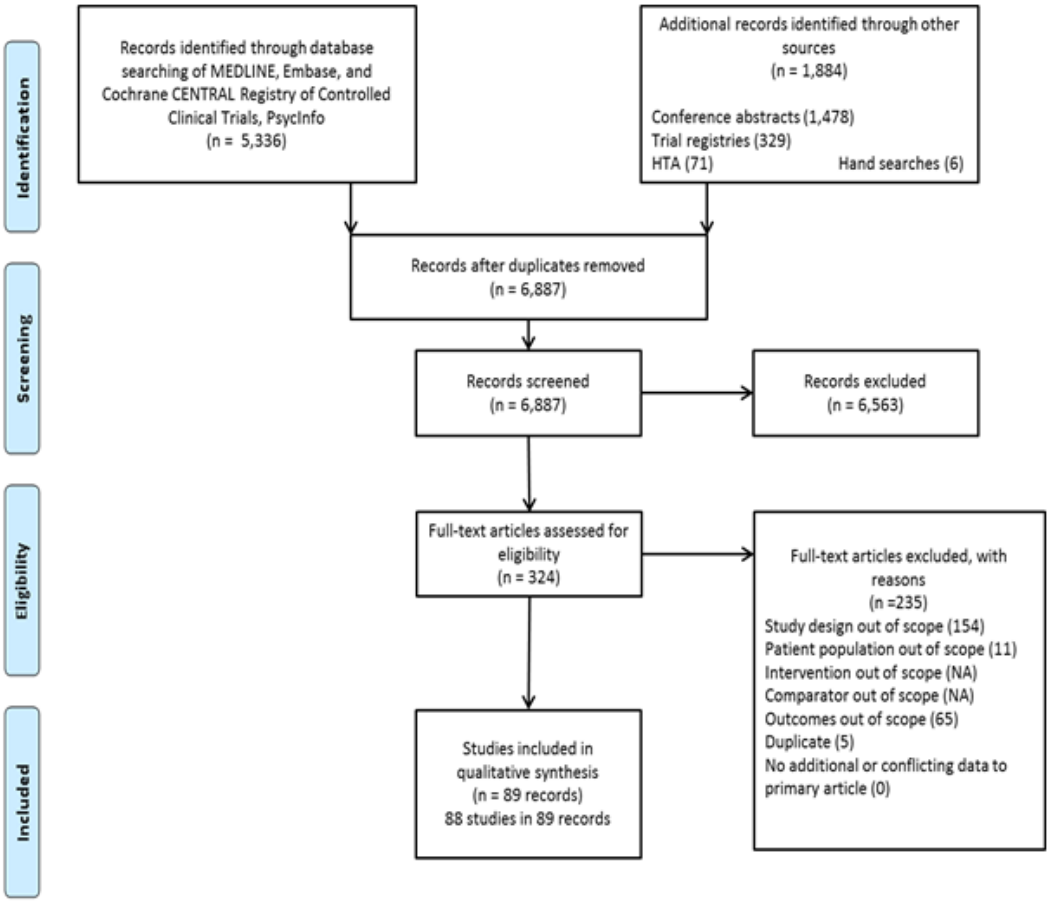
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of a mixed cancer populations not reporting results for melanoma separately
Intervention/Comparators	No restriction by treatment or comparator	Not applicable
Outcomes	• HRQoL data assessed by both generic and disease-specific instruments including the EQ-5D, FACT-BRM, EORTC QLQ-C30, and SF-12 SF-3) • Utility scores • Health state information • Patients satisfaction with treatment	Not applicable

	Inclusion criteria	Exclusion criteria
Study Design	• RCTs, including crossover studies; non-randomised clinical trials; • observational studies (prospective and retrospective cohort studies); • Surveys	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	Not applicable
Date restrictions	Conference proceedings 2013 – Present	Not applicable
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-BRM, Functional Assessment of Cancer Treatment-Biological Response Modifier; RCT, randomised controlled trial; SF, Short Form		

Study selection results for HRQoL evidence

The PRISMA flow diagram for the SLR is presented in Figure 5-28. A total of 7,220 records were retrieved from electronic databases (n=5,336), HTA assessments (n=71), clinical trial registry records (n=329), conference abstracts (n=1,478) and additional records identified from hand searching reference lists of existing systematic reviews (n=6). Following the removal of duplicate records, 6,887 titles and abstracts were screened and from these records, a total of 6,563 studies were excluded. Following the exclusion, 324 full-text records were screened to determine whether they fulfilled the review inclusion criteria and after detailed review, 89 records reporting data for 88 studies were selected as meeting all of the inclusion criteria and were extracted in full.

Figure 5-28: PRISMA flow diagram for HRQoL and Utility evidence



Details of the studies in which HRQoL was measured

Of the 88 studies that were extracted in full, 36 were conducted in patients with stage III – IV melanoma, 45 studies in patients with any stage melanoma, and 7 studies were in mixed cancer populations with results specifically reported for patients with melanoma.

Outcomes assessed included HRQoL, stress and anxiety, depression, fatigue, coping satisfaction with treatment, disease impact, social support/relationships, self-image and health-state utilities.

The most frequently used instruments to assess outcomes were the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-C30 (n=18), the Short Form (SF)-36 (n=9) and the Hospital Anxiety and Depression Scale (HAD) (n=9). Functional Assessment of Cancer Therapy-Melanoma (FACT-M) (n=6), EuroQOL (EQ-5D) (n=5), the State-Trait Anxiety Index (STAI) (n=5) and Beck Depression Inventory (BDI) (n=5), were used less frequently.

Of the 88 studies were identified in the SLR only 8 were deemed relevant to the decision problem (Table 5-10) in that they included a preference based quality of life instrument (e.g. EQ-5D, SF-36, SF-12, SF-6D or HUI)

Table 5-10: Details of the studies in which HRQoL was measured

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Stage III and IV melanoma					
Hatswell 2014[132]	Patients enrolled at 125 centres in 13 countries in North America, South America, Europe, and Africa UK / Utility	IPI+ gp100 IPI only gp100 only	Advanced or metastatic MEL	EORTC-8D SF-6D	<u>EORTC-8D</u> Progression: Pre-progression: 0.803 Post-progression: 0.755 Time to death: 180 or more days to death: 0.831 120 - 179 days to death: 0.771 90 - 119 days to death: 0.763 60 - 89 days to death: 0.720 30 - 59 days to death: 0.679 Under 30 days to death: 0.653 <u>SF-6D</u> Progression: Pre-progression: 0.642 Post-progression: 0.612 Time to death: 180 or more days to death: 0.667 120 - 179 days to death: 0.616 90 - 119 days to death: 0.613 60 - 89 days to death: 0.585 30 - 59 days to death: 0.557 Under 30 days to death:0.544

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Beusterien 2009[130]	UK and Australia / Cross-sectional, standard gamble	NA	Advanced MEL patients	Treatment response: WHO definition for all cancers Toxicity: common grade I/II toxicities from published and unpublished literature, and product inserts for IPI, DTIC, TMZ, IL-2, fotemustine, and IFN-α	<u>Australia and UK</u> Partial response 0.88 Table disease 0.80 Progressive disease 0.52 <u>UK</u> Partial response 0.85 Table disease 0.77 Progressive disease & BSC 0.59
CheckMate 066 2015[133]	ND / Phase III RCT	NA	Patients with advanced MEL	EQ-5D VAS EORTC global health	Non-progressive disease 0.77 Progressive disease 0.68
CheckMate 069 2015[134]	ND / Phase II trial	NA	Patients with metastatic or unresectable MEL	EORTC QLQ-C30 EQ-5D	ND
NICE TA321 2014[1]	UK / Technology submission and appraisal	Dabrafenib DTIC	Unresectable or metastatic MEL	EQ-5D	CR 0.77 PR 0.77 SD 0.77 PD 0.68
NICE TA268 2011[57]	UK / Technology submission and appraisal	IPI BSC, CT or DTIC	Advanced MEL patients	EQ-5D	Progression-free disease 0.81 Progressive disease 0.77
Any stage melanoma					
Mols 2010[135]	NL / Observational	NA	MEL survivors	SF-36 IOC	ND
Tromme 2014	Belgium / Utility	NA	MEL patients	EQ-5D-5L VAS FACT-M	Stage III-T From start of treatment 0.535 Stage IV-R From start of remission 0.796

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Abbreviations: Scale; CT = chemotherapy; DTIC = dacarbazine; EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQOL;; GAD = General; HRQoL health-related quality of life; IFN = interferon; IL=2 = interleukin-2; IPI = ipilimumab; IPQ = Illness Perception Questionnaire; ISSS = Illness-Specific MEL = melanoma; ; ND = not documented; NL = Netherlands;; SF = Short Form; -Short Form;; TMZ = temozolomide; UK = United Kingdom; US = United States; VAS = Visual Analogue Score; VFB					

Key differences between values derived from the literature search and those reported in or mapped from the clinical trials

The trial based HRQoL data is inconsistent with the NICE reference case and has not been used in the economic analysis. Consequently, HRQoL data from the literature has been used in the economic model (Table 5-10).

Adverse events

AEs associated with therapy can have an impact on the quality of life of patients receiving treatment for metastatic melanoma.

T-VEC has a largely manageable safety profile with the most frequent events being pyrexia, chills, flu-like symptoms, and injection site reactions, most of which were non-serious and mild to moderate in severity (Section 4.13). Given the low incidence of grade ≥3 AEs in the OPTiM trial (2.1%), the model considers grade ≥3 AEs with an incidence of ≥2% as a conservative measure. This is in contrast with the ipilimumab NICE TA (TA319)[2] where the model considered grade ≥3 AEs with an incidence of ≥3%. This approach was deemed appropriate in this context given the very low incidence of adverse events observed in the OPTiM trial for T-VEC; the only AE of grade ≥3 occurring in 2.1% of patients was cellulitis. When considered in the context of the severity of uncontrollable metastatic melanoma, this was not considered to impact on patient's HRQoL. It is noteworthy that grade 1 or 2 AEs were not included in the model because it was assumed they would not be associated with any meaningful management costs or impact HRQoL. This approach was accepted by the appraisal committee in TA268[2].

The incidence rates of AE's included in the model are presented in Table 5-11. The incidence of all AEs was assumed to be annual and they were assumed to last one day; AE-related QALYs were calculated by multiplying the incidence of each AE (i.e., the probability of occurring) by its duration and the day equivalent of the disutility for that AE. These were then summed across all AEs and subtracted from the overall QALY gain for each treatment.

Table 5-11: Incidence of grade ≥3 AEs with an incidence of ≥2%

Grade ≥3 AEs	T-VEC[a] (%)	IPI[b] (%)
Anaemia	-	3.1
Cellulitis	2.1	-
Colitis	-	5.3
Constipation	-	2.3
Diarrhoea	-	5.3
Dyspnea	-	3.9
Fatigue	-	6.9
Headache	-	2.3
Nausea	-	2.3
Vomiting	-	2.3

AE, adverse events; IPI, ipilimumab; T-VEC, talimogene laherparepvec

[a] Source: Andtbacka et al. (2015)[79]. Includes AEs with an incidence ≥2%

[b] Source: Hodi et al. (2010)[72]. Includes AEs with an incidence of ≥3%

Health-related quality-of-life data used in cost-effectiveness analysis

Health states in terms of HRQoL in the cost-effectiveness analysis.

QALYs were calculated using area under the curve (AUC) methods. The Health State Utility Value (HSUV) for non-PD was assigned to patients in the non-PD health state. The HSUV for PD was assigned to patients in the PD health state (i.e., the difference between the OS and PFS curves in each cycle). The QALYs for non-PD and PD were summed by treatment arm over the 30-year horizon. The model also included disutilities for grade ≥3 AEs, obtained from a preference elicitation study (Appendix 1.7). Only one grade ≥3 AE, cellulitis (2.1%), was reported for patients on the T-VEC arm in the OPTiM trial[79]. The disutilities ≥3 AEs associated with the comparators are shown in Table 5-12.

Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness

Quality of life was assumed to remain constant in each health state.

Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

Description of how and why health state utility values used in the cost effectiveness analysis have been adjusted, including the methodologies used

Not applicable.

Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

As described in Section 5.4 only grade ≥3 AE's with an incidence of ≥2% were modelled for both T-VEC and ipilimumab.

Summary of utility values chosen for the cost-effectiveness analysis

Utility values used in the cost-effectiveness analysis are presented in Table 5-12.

Table 5-12: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Source
Base-case values				
CR	0.77 (0.011)	0.75-0.79	Section 5.4	TA321[1]
PR	0.77 (0.011)	0.75-0.79		
SD	0.77 (0.011)	0.75-0.79		
PD	0.68 (0.084)	0.52-0.85		
Alternative values used in scenario analyses				

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Source
CR	0.84 (0.011)	0.82-0.86	Section 5.4	Amgen, 2014 (utility study for advanced melanoma)[136]
PR	0.73 (0.011)	0.71-0.75		
SD	0.69 (0.011)	0.67-0.71		
PD	0.45 (0.084)	0.29-0.61		
CR	0.85 (0.011)	0.83-0.87	Section 5.4	Beusterin et al 2009[130]
PR	0.85 (0.011)	0.83-0.87		
SD	0.77 (0.011)	0.75-0.79		
PD	0.59 (0.084)	0.43-0.75		
CR	0.81 (0.011)	0.79-0.83	Section 5.4	TA268[57]
PR	0.81 (0.011)	0.79-0.83		
SD	0.81 (0.011)	0.79-0.83		
PD	0.77 (0.084)	0.61-0.93		
Disutilities associated with AEs				
Anaemia	0.09 (0.003)	0.083-0.097	Section 5.4	Amgen, 2014 (utility study for advanced melanoma) [136]
Cellulitis	0.12 (0.005)	0.111-0.129		
Colitis	0.26 (0.010)	0.241-0.280		
Constipation	0.14 (0.005)	0.130-0.151		
Diarrhea	0.11 (0.004)	0.102-0.118		
Dyspnea	0.11 (0.004)	0.102-0.118		
Fatigue	0.05 (0.002)	0.046-0.054		
Headache	0.16 (0.006)	0.148-0.172		
Nausea	0.26 (0.010)	0.241-0.280		
Vomiting	0.26 (0.010)	0.241-0.280		

AE, adverse event; CR, complete response; PD, progressive disease; PR, partial response, SD, stable disease

Details if clinical experts assessed the applicability of the health state utility values available or approximated any of values

Not applicable.

5.5 Cost and healthcare resource use identification, measurement, and valuation

Parameters used to estimate cost-effectiveness

A summary of the variables used in the cost-effectiveness analysis is presented in Section 5.6.

Resource identification, measurement, and valuation studies

A SLR was conducted in September 2015 to systematically identify, critically review, and summarise studies evaluating the cost-effectiveness of treatments in advanced melanoma. The literature review was subsequently used to inform the cost-effectiveness model structure and some of the key inputs used in this appraisal

Search strategy

The search included peer-reviewed journal articles, HTA documents, and data from relevant conference proceedings. Full details are provided in Appendix 1.2. The following databases were searched for relevant studies:

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.
- EconLit (OvidSP):1886 to August 2015
- NHSEED (OvidSP):2nd Quarter 2015

Supplementary searches were undertaken for the following trials registers from inception to March 2015:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- EU Clinical Trials Register (EUCTR) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- PharmaNet.Bund (http://www.pharmnet-bund.de/static/de/index.html)
- National Institutes of Health (NIH) Clinical Trial Registry (CTR)
- Australian New Zealand Clinical Trials Registry (ANZCTR) (http://www.anzctr.org.au/TrialSearch.aspx)

Further supplementary searches were undertaken in relevant conference abstracts from 2013 to present:

- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(http://www.ispor.org/)
- European Association of Dermato Oncology (EADO) (http://www.eado.org/)
- European Cancer Congress (ECC) (http://www.esmo.org/Conferences/European-Cancer-Congress-2015)
- Society of Melanoma Research (SMR) (http://www.societymelanomaresearch.org/)

- Perspectives in Melanoma (PIM) (http://imedex.com/perspectives-melanoma-conference/)

Additionally, a manual search of HTA websites was also under taken for the:

- UK:
  - NICE (www.nice.org.uk)
  - AWMSG (http://www.awmsg.org/app/search?execution=e1s1)
  - SMC (http://www.scottishmedicines.org.uk/Home)
- Canada
  - CADTH (http://www.cadth.ca)

Study selection

Study inclusion was not limited by language. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 5-13.

Table 5-13: Study inclusion and exclusion criteria

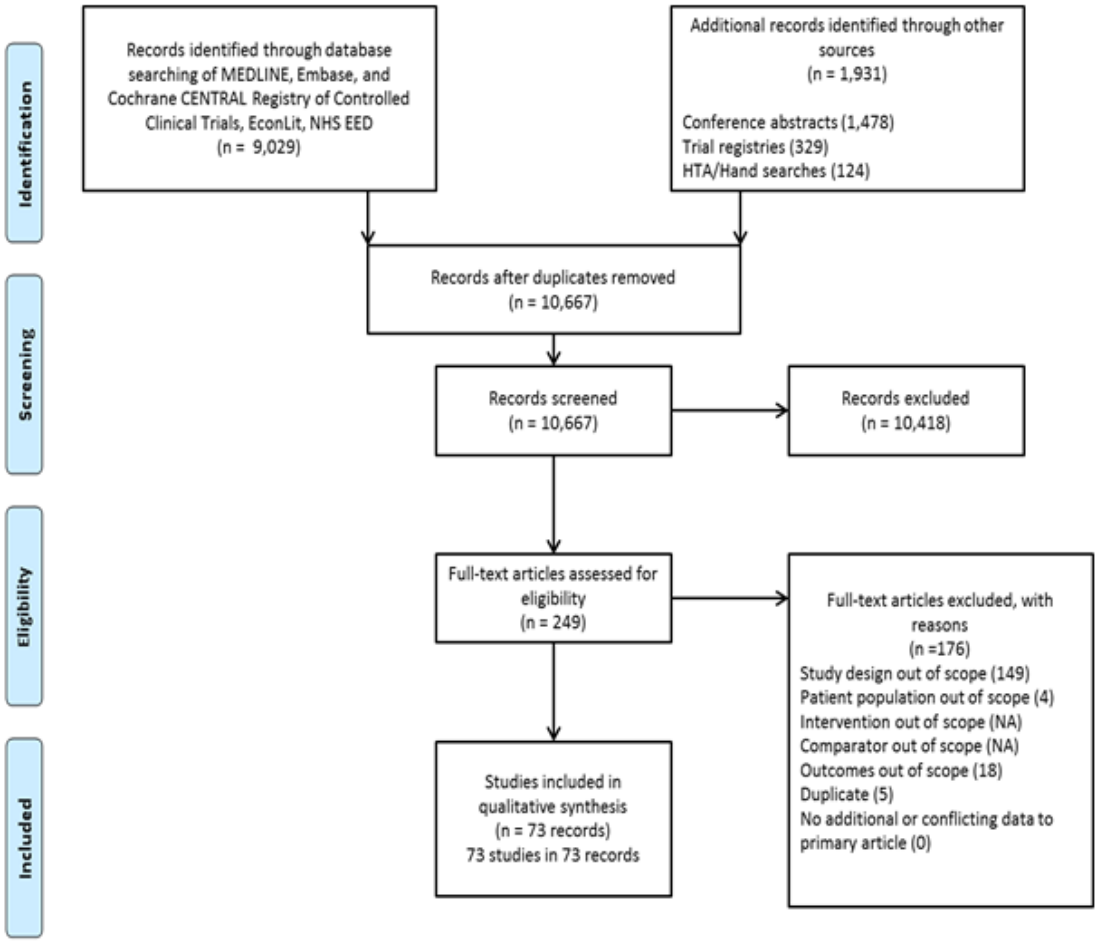
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of a mixed cancer populations not reporting results for melanoma separately
Intervention/ Comparators	There was no restriction by treatment or comparator.	Not applicable
Therapeutic Area/ Conditions of Interest	Melanoma	Not applicable
Outcomes	Global healthcare resource use and global healthcare cost data	Not applicable
Study Design	Published cost or resource use documentation studies	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	
Date restrictions	Not applicable	Not applicable

Study selection results for economic evaluation evidence

The PRISMA flow diagram for the SLR is presented in Figure 5-29. A total of 9,029 records were retrieved from electronic databases (n=9,029), HTA assessments (n=124), clinical trial registry records (n=329) and conference abstracts (n=1,478). Following the removal of duplicate records, 10,667 titles and abstracts were screened and from these records, a total of 10,418 studies were excluded. 249 full-text records that were remaining were screened to

determine whether they fulfilled the review inclusion criteria and after detailed review, 73 records reporting data for 73 studies were selected as meeting all of the inclusion criteria and were extracted in full.

Figure 5-29: PRISMA flow diagram for Resource Use



Description of Identified studies

To ensure the SLR captured sufficient relevant information to populate the economic model, the population criteria considered were broader than advanced melanoma and there was no restriction on the intervention. The majority of studies were conducted in the United States (n=24) and the United Kingdom (n=11), with other studies conducted in Europe (n=26), North America (n=4), Australia (n=3) and New Zealand (n=1).

The types of healthcare resource use examined included pharmacy resources (including drug costs, drug management and management of toxicity); surgical resources (including excisions and biopsies); laboratory resources (such as complete blood count and complete metabolic panels); imaging resources (such as computed tomography and positron emission tomography scans and x-rays; in-patient resources (such as hospitalisations, emergency room visits); outpatient resources including office visits, hospice resources including palliative and end-of-life care, and all associated costs.

Of the 11 UK sources, eight were deemed relevant to the decision problem and the decision making process in England and are summarised in Table 5-14.

The only study to formally report resource utilisation in terms of inpatient, outpatient and hospice care requirements is the MELODY study[137,138] and it represents the largest single study of resource utilisation in melanoma (n=220) reporting resource utilisation for a UK-specific cohort.

Table 5-14: Summary list of published cost-and resource use studies

First author, year	Study design	Intervention	Source for costing data	Cost type
NICE TA319 2014[2]	Technology submission and appraisal, including cost-utility analysis	IPI DTIC VEM	NHS and PSSRU references and Oxford outcomes Melanoma Resource Use report For the identification of IPI administration costs, existing CT delivery HRGs to cost its administration Existing literature	Treatment-specific costs Melanoma Resource Use
NICE TA269 2012[58]	Technology submission and appraisal, including cost-utility analysis	VEM DTIC	BRIM-3 trial, Robert trial, US SEER for patients with melanoma, the main sources of cost data are the NHS Reference Cost Schedule (09-10), the British National Formulary and the MS submitted for the NICE appraisal of IPI	Drug acquisition and administration Testing for BRAF V600 Cost of disease relate to health states and treating AEs
NICE TA321 2014[1]	Technology submission and appraisal, including cost-utility analysis	Dabrafenib DTIC VEM	Clinical data and HRQoL from BREAK3 trial; Data for VEM from BRIM-3 trial.	Drug costs, dispensing costs, administration costs, anti-cancer therapy after the study costs.
NICE TA268 2012[57]	Technology submission and appraisal, including cost-utility analysis	IPI BSC	MDX 010-20 trial, 10 economic evaluations; drug costs retrieved from British national formulary	Drug acquisition and administration costs Cost of the disease
Johnston 2012[137]	Retrospective analysis based on Melody (multinational, observational, longitudinal and retrospective study of	Systemic therapy BSC	UK cohort Hospitalisation: NHS Hospice: UK Consumer Price Indices Outpatient: NHS	Hospitalisation (per diem) Hospice (per diem) Outpatient (per visit)

First author, year	Study design	Intervention	Source for costing data	Cost type
	advanced melanoma patients)			
NICE TA357 2015[59]	Technology submission and appraisal, including cost-utility analysis	PEM BSC	KEYNOTE-002 Schadendorf et al. 2015 Balch et al. 2001 American Joint Committee on Cancer	Costs of treatment, monitoring and follow-up, management of complications and adverse events, and terminal care.
Lorigan 2014[138]	Multinational, observational, retrospective, longitudinal survey	ND	UK data collected from a multinational, observational, retro, longitudinal survey	Any hospitalisation Any hospice care Any outpatient care
Linker 2013[139]	Retrospective cost attribution analysis	IFN non-IFN	Medical records; British National Formulary; National Institute for Health Research costing template"	

AE, adverse event; BSC, best supportive care; DTIC, dacarbazine; HRG, healthcare resource group; IFN, interferon; IPI, ipilimumab; ND, not documented; NHS, national health service; PEM, pembrolizumab; PSSRU, Personal Social Services Research Unit; SEER, Surveillance Epidemiology and End Results registry; VEM, vemurafenib

NHS reference costs or payment-by results (PbR) tariffs

T-VEC is administered via intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. It is anticipated that administration of T-VEC will take place in a limited number of centres specialising in the treatment of skin cancers and it will be administered in an outpatient setting in a designated side room.

The HRG codes for chemotherapy delivery are described in Table 5-15. It is assumed that the cost of administering T-VEC would be equivalent to that of ipilimumab.

There are no HRG codes specific to T-VEC and there are no other chemotherapy treatments administered in a similar fashion to T-VEC, so it was therefore assumed that the cost of administering T-VEC would be equivalent to that of ipilimumab (HRG code SB13Z). This assumption is further supported by a study conducted by Amgen to understand the administration cost of T-VEC[140] (further details of the study are provided in Appendix 1.8).

Table 5-15: HRG codes for chemotherapy delivery

HRG code	Description
SB11Z	Deliver exclusively Oral Chemotherapy
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
SB15Z	Deliver subsequent elements of a chemotherapy cycle
SB16Z	Procure Chemotherapy drugs for regimens not on the national list
SB17Z	Deliver chemotherapy for regimens not on the national list
Source: NHS Reference Costs 2013-14[141]	

Clinical experts input

Resource costing study

The model incorporated data on healthcare resource utilisation for routine treatment, disease progression, and palliative care.

A treatment patterns survey and a costing study[140] were conducted to estimate healthcare resource utilisation associated with adopting T-VEC into routine clinical practice within the NHS. The study identified phases of resource use between active treatment and death in the advanced melanoma treatment pathway and was based on previous technology appraisals, an online survey of physicians, and international treatment guidelines.

Healthcare resource utilisation for BSC was derived from a NICE TA268 since the costing study did not distinguish BSC from palliative care[57].

For the costing study, a questionnaire was developed listing the resources such as consultations, monitoring, hospital visits, and surgical procedures that could be used in each

of these phases. Estimates of the magnitude (i.e., the percentage of patients utilising each resource item) and frequency of resource use per 3 or 6 months in clinical practice were obtained through consensus panels comprising experienced oncologists who treated patients with advanced melanoma. These were converted to estimated average monthly resource use per patient, as shown in Table 5-16.

In the non-PD health state, it was assumed that all patientswould receive routine care, irrespective of active treatment and response category (complete response, partial response, stable disease). This is a conservative assumption as it is plausible that patients who achieve a complete response may not require any routine care or require less than patients who achieve only partial response or have stable disease. As for patients with PD, all patients in non-PD health states were considered to receive BSC, irrespective of prior active treatment.

As described previously, monthly resource use for BSC was derived from NICE TA268[57] and calculated by multiplying the estimates of the magnitude by the frequency of BSC resource use. The data extracted from NICE TA268 are summarised in Table 5-16. The healthcare resource utilisation for terminal care was based on a microcosting study by the King's Fund[142]. In the model, patients who died were assumed to receive terminal care immediately prior to death.

Table 5-16: Monthly mean healthcare resource use per patient

Item	Routine treatment (units)	On progression (units)	Best supportive care[a] (units)	Palliative care (units)
Outpatient visits				
Medical oncologist	0.00	1.00	1.63	0.67
Radiation oncologist	0.03	0.10	0.06	0.00
General practitioner	0.33	0.00	0.08	0.53
Psychologist	0.03	0.00	0.00	0.05
Palliative care physician/nurse	0.00	0.00	0.00	0.13
Surgeon	0.02	0.05	0.03	0.02
Dermatologist	0.00	0.00	0.00	0.02
Oncology nurse	0.60	0.00	0.00	0.20
Inpatient stay				
Oncology ward	0.25	0.20	0.07	0.33
Day hospital	0.25	0.00	0.00	0.13
Emergency department	0.03	0.00	0.00	0.05
Home care				
Palliative care physician/nurse	0.00	0.00	0.00	0.50
Home aide visits	0.00	0.00	0.00	3.47

Item	Routine treatment (units)	On progression (units)	Best supportive care[a] (units)	Palliative care (units)
Laboratory tests				
Complete blood count	1.00	0.00	1.30	0.00
Complete metabolic panel	1.00	0.00	1.24	0.00
LDH measurement	0.00	0.00	1.24	0.00
Radiological exams				
Brain MRI	0.03	0.05	0.06	0.00
PET-CT scan	0.02	0.00	0.01	0.00
Bone scintigraphy	0.02	0.00	0.00	0.00
Chest radiograph	0.03	0.05	0.33	0.00
Brain CT	0.00	0.05	0.02	0.00
Whole-body CT	0.33	0.00	0.00	0.00
CT scan of abdomen/pelvis	0.00	0.00	0.38	0.00
CT scan of chest	0.00	0.00	0.38	0.00
Echography	0.00	0.00	0.04	0.00
Radiation oncology				
Stereotactic radiosurgery	0.00	0.20	0.00	0.00
Whole-brain radiation	0.00	1.00	0.00	0.00
Radiotherapy	0.07	0.20	0.00	0.00
Procedures				
Neurosurgery	0.00	0.10	0.00	0.00
Surgery (including biopsy and histopathology)	0.02	0.05	0.00	0.02

CT = computed tomography; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography.[a]

Source: NICE TA268, 2011[57]; Amgen, 2014[140]

Intervention and comparators' costs and resource use

The assumptions around dosing and consequent costs of treatment for T-VEC and the comparator treatments are described below.

Drug Acquisition Costs

The drug costs for T-VEC and ipilimumab are presented in Table 5-17 and the assumptions around dosing presented in Table 5-18. The drug acquisition cost for ipilimumab is based on its NHS list price and does not reflect the confidential PAS that is available for ipilimumab in the NHS. The drug acquisition cost for T-VEC is based on the anticipated list price of T-VEC. A PAS has been proposed for T-VEC and is currently under consideration by PASLU.

Table 5-17: Treatment cost per vial/pack

Treatment	Vial volume (mL)/ pack size	Cost per vial	Source
T-VEC	10^6pfu/mL x1mL vial 10^8pfu/mL x1mL vial	Anticipated list price £1,445 £1,445	BNF 2015[143]
Ipilimumab	10mL (50mg) vial 40mL (200mg) vial	NHS list price £3,750 £15,000	BNF 2015[143]

Table 5-18: Treatment Dosing Schedule*

Treatment	Dosage (including wastage)	Mean duration of treatment	Source
T-VEC	Cycle 1 (21 days): [redacted] vials of 10^6 pfu/mL Subsequent cycles (every 14 days): [redacted] vials of 10^8 pfu/mL	[redacted]	OPTiM[79]
Ipilimumab	52.20 mL every 3 weeks (1.22 x 10mL vials and 1.00 x 40mL vial)	10.50 weeks (3.5 administrations)	BMS (2015)[47]; Hodi et al. (2010)[72]
*All reported doses in the base case assume drug wastage			

T-VEC dose and treatment duration

The OPTiM study included 163 patients in the TVEC arm with stage IIIB-/IVM1a metastatic melanoma with non-visceral metastases[79]. Patients in the OPTiM trial remained on treatment for at least 6 months even in the event of disease progression (unless intolerability or alternate therapy was required based on assessment of the patient's clinical status)[79]. This is reflected in the anticipated marketing authorisation and is also reflected in the estimated of T-VEC dose and treatment duration.

In the OPTiM trial, an accelerated dosing schedule could be invoked, in which the frequency of injections into any progressing lesion(s) could be increased to once per week for 4 weeks and up to three sets of four accelerated injections could be given (as long as after each set of four accelerated injections, clinically relevant disease progression did not occur and there was still residual tumour to inject[79]. Accelerated dosing is not recommended in the anticipated license for T-VEC (refer to SPC; (Appendix 1.1). It is noteworthy that accelerated doses made up a very small proportion of doses administered (4.5%) in the trial and patients who received accelerated doses in the trial had poorer survival outcomes compared to patients who did not receive accelerated dosing. In routine clinical practice, it is anticipated that clinicians would not increase dosing frequency of T-VEC especially given that alternatives treatment options are available. Consequently the base-case analysis excludes accelerated doses.

In the OPTiM trial patients who had successfully completed treatment were eligible to enter into an extension study if they did not have disease progression during the OPTiM study or had a CR but developed new lesions within 12 months[81]. In the extension study patients continued with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity. A small proportion of patients (9.8%) on the T-VEC arm entered the extension phase. 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 (Section 5.5).

Individual patient-level data (IPD), relating to the use of T-VEC from the OPTiM study and the extension phase, was used to calculate the mean number of whole vials per injection day including wastage. This approach accounts for the observed numbers of whole vials used in order to accurately estimate the drug acquisition cost.

Mean injection days (i.e., visits where a patient received treatment) and mean number of whole vials per injection for T-VEC are reported in Table 5-19. The total mean number of vials is calculated using the total number of whole vials received by each patient over the time period.

The base case which excludes accelerated dosing but conservatively includes extension phase dosing, estimates a total number of [redacted] whole vials of T-VEC used in the model (Table 5-19).

Table 5-19: T-VEC dose assuming wastage used in the cost-effectiveness analysis (based on proposed licensed indication Stage IIIB-IVM1a)

T-VEC Dose Scenarios	First Dose (mL)	Subsequent Doses (mL)	Mean number of injections (including first injection)	Total number of vials (mL)
Exclude accelerated doses, exclude extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]
Exclude accelerated doses, include extension phase doses (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Include accelerated doses, include extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]
Include accelerated doses, exclude extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]

Ipilimumab

The acquisition cost of ipilimumab is £3,750.00 per 10-mL vial and £15,000.00 per 40-mL vial[143]. For the base case, a mean number of 5.22 whole vials (including wastage) of ipilimumab per administration with 3.5 administrations was used as per TA319[2]. Although this estimate is not in line with the SPC and is indeed lower than the SPC recommended regimen, this conservative estimate (in favour of ipilimumab) has been used in the base case in the economic model.

Drug administration costs

The NHS reference costs for administration of ipilimumab and T-VEC are presented in Table 5-20. Both T-VEC and ipilimumab are considered to be administered as a day case, and the costs of administration are assumed to be similar at £317 (HRG code SB13Z).

Table 5-20: NHS reference costs and PSSRU costs – administration of treatments

Description	Source	Unit Price
Deliver more complex parenteral chemotherapy at first attendance- daycase	NHS Reference Costs[141] 2013/14 SB13Z	£316.95
NHS, National Health Service; PSSRU, Personal Social Services Research Unit		

Health-state unit costs and resource use

The systematic review of economic literature (Section 5.5), identified the MELODY study[137,138], a large study of resource utilisation in melanoma, reporting resource utilisation for a UK-specific cohort. These data were previously reported in NICE TA319[2] and subsequently in NICE TA357[59]. The following limitations relating to the MELODY study were noted in these appraisals:

- The study predated the new melanoma treatments currently approved and recommended.
- Patients were recruited 8-10 years ago, and as such the clinical landscape may differ considerably to UK practice today, particularly given the availability of ipilimumab and available treatments for BRAF-mutation positive melanoma.
- Dacarbazine, the most widely used treatment among patients in the MELODY study[138], is now used only when no active treatment is available.

Given the limitations of the MELODY study, Amgen commissioned a costing study to collect data on the costs associated with HRU use throughout the treatment pathway for advanced melanoma[140] described in Section 5.5. Using published literature and clinician input, four treatment phases were identified: active systemic treatment (pre-progression); disease progression; best supportive care (BSC)/palliative care; and terminal care. HRU elements were identified for each phase and estimates of the magnitude and frequency of use in clinical practice were obtained through a UK Delphi panel, comprising seven experienced oncologists.

The costs were then applied in the model as follows:

- Routine care costs: the unit costs of HRU for routine care of patients were multiplied by the monthly estimates of HRU to derive a monthly cost of routine treatment, which then

was converted to weekly costs and subsequently applied by cycle for patients with non-PD.

- On-progression costs: the unit costs of HRU for patients switching to PD were multiplied by the estimates of HRU. This was applied as a one-time cost for patients whose disease progressed.
- BSC costs: the unit costs of HRU for patients in BSC were multiplied by the monthly estimates of HRU for BSC. The monthly costs were converted to weekly costs and then applied by cycle for patients with PD until the administration of palliative care.
- Palliative care costs: the unit costs of HRU for patients in palliative care were multiplied by the monthly estimates of HRU for palliative care. The monthly costs were converted to weekly costs and then applied by cycle for patients with PD for 3 months prior to death. These costs were calculated separately from terminal care costs, to avoid overlapping of costs.
- Terminal care cost: the one-time cost of terminal care was applied to all patients who died.

The costs of disease management in the non-PD and the PD health states were irrespective of active treatment. Table 5-21 presents a summary of the resource use costs that are applied in the model

Table 5-21: Summary of resource use costs

Health state	Cost	Frequency
Non-progressive disease		
Routine treatment	£86.52	Per cycle
Progressive disease		
On progression	£1,198.50	One-off
Best supportive care	£91.24	Per cycle
Palliative care	£192.03	Per cycle
Terminal care	£6,105.00	One-off

The impact of the cost estimates for the non-progressive disease health state and the terminal care cost are explored in scenario analyses (Section 5.8). The impact of the BSC cost estimate is explored in the deterministic sensitivity analysis (Section 5.8).

Table 5-22 presents the detailed monthly HRU estimates and the corresponding unit costs according to health states. All data were obtained from NHS reference costs[141], the Personal Social Services Research Unit (PSSRU)[144], and NICE's TA 268[57]. A one-off cost of £6,105 for terminal care was obtained from the King's Fund[142]. All unit costs were inflated to 2013-2014 values, using the published inflation index from the PSSRU[144].

Table 5-22: List of health states and associated costs in the economic model

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
Non-progressive disease						

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
Routine treatment pre-progression: outpatient visits						Section 5.5
	Radiation oncologist	0.03	126.00	NHS Reference Costs (2013-2014)	800	
	General practitioner	0.33	46.00	PSSRU (2014)	NA	
	Psychologist	0.03	138.00	PSSRU (2014)	NA	
	Surgeon (cosmetic/ plastic)	0.02	93.00	NHS Reference Costs (2013-2014)	160	
	Oncology nurse	0.60	80.00	PSSRU (2014)	NA	
Routine treatment pre-progression: inpatient stay						Section 5.5
	Oncology ward	0.25	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Day hospital	0.25	513.00	NHS Reference Costs (2013-2014) (day case)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Emergency department	0.03	147.00	NHS Reference Costs (2013-2014), category 2 treatment (accident and emergency services)	VB07Z	
Routine treatment pre-progression: laboratory tests						Section 5.5
	Complete blood count	1.00	3.00	NHS Reference Costs (2013-2014)	DAPS05	
	Complete metabolic panel	1.00	1.00	NHS Reference Costs (2013-2014)	DAPS04	
Routine treatment pre-progression: radiological exams						Section 5.5
	Brain MRI	0.03	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
	PET-CT scan	0.02	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	Bone scintigraphy	0.02	183.00	NHS Reference Costs (2013-2014)	RA35Z	
	Chest radiograph	0.03	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Whole-body CT	0.33	146.00	NHS Reference Costs (2013-2014)	RA14Z	
Routine treatment pre-progression: radiation oncology						Section 5.5
	Radiotherapy	0.07	533.00	NHS Reference Costs (2013-2014)	SC45Z/SC46Z	
Routine treatment pre-progression: procedures						Section 5.2
	Surgery (including biopsy and histopathology)	0.02	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	
Progressive disease						
On progression: outpatient visits						Section 5.5
	Medical oncologist	1.00	140.00	NHS Reference Costs (2013-2014)	370	
	Radiation oncologist	0.10	126.00	NHS Reference Costs (2013-2014)	800	
	Surgeon (cosmetic/ plastic)	0.05	93.00	NHS Reference Costs (2013-2014)	160	
On progression: inpatient stay						Section 5.5
	Oncology ward	0.20	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
On progression: radiological exams						Section 5.5
	Brain MRI	0.05	170.00	NHS Reference Costs (2013-	RA01A/RA02A/RA03	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				2014)	Z	
	Chest radiograph	0.05	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Brain CT	0.05	104.00	NHS Reference Costs (2013-2014)	RA08A/RA09A/RA10Z	
On progression: radiation oncology						Section 5.5
	Stereotactic radiosurgery	0.20	978.00	NHS Reference Costs (2013-2014)	SC52Z	
	Whole-brain radiation	1.00	644.00	NHS Reference Costs (2013-2014)	SC46Z	
	Radiotherapy	0.20	533.00	NHS Reference Costs (2013-2014)	SC45Z/SC46Z	
On progression: procedures						Section 5.5
	Neuro-surgery	0.10	£181.00	NHS Reference Costs (2013-2014)	150	
	Surgery (including biopsy and histopathology)	0.05	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	
Best supportive care: outpatient visits						Section 5.5
	Medical oncologist	1.63	140.00	NHS Reference Costs (2013-2014)	370	
	Radiation oncologist	0.06	126.00	NHS Reference Costs (2013-2014)	800	
	General practitioner	0.08	46.00	PSSRU (2014)	NA	
	Surgeon (cosmetic/ plastic)	*0.03*	*93.00*	*NHS Reference Costs (2013-2014)*	*160*	
Best supportive care: inpatient stay						Section 5.5
	Oncology ward	0.07	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				stay) excess bed days)	JD07H/JD07J/JD07K	
Best supportive care: laboratory tests						Section 5.5
	Complete blood count	1.30	3.00	NHS Reference Costs (2013-2014)	DAPS05	
	Complete metabolic panel	1.24	1.00	NHS Reference Costs (2013-2014)	DAPS04	
	LDH measurement	1.24	1.00	NHS Reference Costs (2013-2014)	DAPS04	
Best supportive care: radiological exams						Section 5.5
	Brain MRI	0.06	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	PET-CT scan	0.01	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	Chest radiograph	0.33	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Brain CT	0.02	104.00	NHS Reference Costs (2013-2014)	RA08A/RA09A/RA10Z	
	CT scan of abdomen/pelvis	0.38	104.00	NICE TA319	RA08A/RA09A/RA10Z	
	CT scan of chest	0.38	104.00	NICE TA319	RA08A/RA09A/RA10Z	
	Echography	0.04	65.00	NHS Reference Costs (2013-2014)	RA60A	
Palliative care: outpatient visits						Section 5.5
	Medical oncologist	0.67	140.00	NHS Reference Costs (2013-2014)	370	
	General practitioner	0.53	46.00	PSSRU (2014)	NA	
	Psychologist	0.05	138.00	PSSRU (2014)	NA	
	Palliative care physician/nurse	0.13	143.00	NHS Reference Costs (2013-2014)	SD04A	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
	Surgeon (cosmetic/ plastic)	0.02	93.00	NHS Reference Costs (2013-2014)	160	
	Dermatologist	0.02	98.00	NHS Reference Costs (2013-2014)	330	
	Oncology nurse	0.20	80.00	PSSRU (2014)	NA	
Palliative care: inpatient stay						Section 5.5
	Oncology ward	0.33	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Day hospital	0.13	513.00	NHS Reference Costs (2013-2014) (day case)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Emergency department	0.05	147.00	NHS Reference Costs (2013-2014), category 2 treatment (accident and emergency services)	VB07Z	
Palliative care: home care						Section 5.5
	Palliative care physician/nurse	0.50	153.00	PSSRU (2014)	NA	
	Home aide visits	3.47	124.00	PSSRU (2014)	NA	
Palliative care: procedures						Section 5.5
	Surgery (including biopsy and histopathology)	0.02	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	Section 5.5
Death						
Terminal care	Total one-off cost	NA	6105.00	Improving choice at end of life,	NA	Section 5.5

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				Kings Fund (2008); inflated to 2014		

Abbreviations: CT, computed tomography, LDH, lactate dehydrogenase, MRI, magnetic resonance imaging; NA, not applicable; NHS, National Health Service; PET, positron emission tomography, PSSRU, Personal Social Services Research Unit.

Source: Addicott and Dewar 2008[142]; Department of Health 2014[141]; NICE 2014 (TA319)[2]; PSSRU 2014[144]

Adverse events unit costs and resource use

Costs for managing AEs were included for all grade 3 or 4 AEs with an incidence of at least 2% in patients receiving any of the treatment options. These AEs were assumed to occur once in the model and persist for 1 day (Section 5.3.3). The costs were mainly derived from NICE TA319[2] and NICE TA269[58], were inflated to the present year and are consistent with those reported in TA357[59]. All costs for managing AEs that are included in the model are presented in Table 5-23.

The costs for managing nausea and vomiting were assumed to be the same as for managing diarrhea, and the cost for managing anaemia was assumed to be the same for managing fatigue. These assumptions are consistent with NICE TA357[59]. Costs for managing cellulitis, constipation, or headache were not available from previous submissions, so the cost of managing cellulitis was assumed to be the same for managing rash in NICE TA269[58]. and the cost for managing headache was assumed to be the same as for managing pain in NICE TA357[59]. The cost of managing constipation and dyspnea was assumed to be £0 based on NICE TA319[2].

It should be noted that all endocrine disorders were included in NICE TA269[58] because they are known to be a serious event associated with treatment with ipilimumab. However, endocrine disorders were not included in our model because the incidence was less than 2% (0.4%). The omission of endocrine disorders was considered to be a conservative assumption when comparing AE costs with T-VEC.

Table 5-23: List of adverse reactions and summary of costs in the economic model

AEs	Items	Value	Source
Anaemia	Inpatient cost	£596.38 (50%)	Cost assumed to be the same as for fatigue in NICE TA319
	Outpatient cost	£156.84 (50%)	
	Average cost per patient	£376.61	
Cellulitis	NR	£137.31	Cost assumed to be the same as for rash in NICE TA269 and inflated to 2014 cost
Colitis	Inpatient cost	£1,011.21 (100%)	NICE TA319 inflated to 2014 costs
Constipation	NA	£0	Cost assumed to be £0
Diarrhoea	Inpatient cost	£838.46 (50%)	NICE TA319 inflated to 2014 costs
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£491.26	
Dyspnoea	NA	£0	NICE TA319; cost assumed to be £0
Fatigue	Inpatient cost	£596.38 (10%)	NICE TA319 inflated to 2014 costs
	Outpatient cost	£156.84 (90%)	
	Average cost per patient	£200.79	
Headache	Outpatient cost	£171.86 (100%)	Cost assumed to be the same as for pain in NICE TA357
Nausea	Inpatient cost	£838.46 (50%)	Cost assumed to be the same as for diarrhoea in NICE TA319
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£213.49	
Vomiting	Inpatient cost	£838.46 (50%)	Cost assumed to be the same as for diarrhoea in NICE TA319
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£213.49	

AE, adverse event; NA, not applicable; NHS, National Health Service; NR, not reported; PPE, palmar-plantar erythrodysesthesia

Source: NICE TA269[58]; NICE TA319[2]; NICE TA357[59]

Miscellaneous unit costs and resource use

Not applicable.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

A list of parameters used in the cost-effectiveness model is detailed in Appendix 1.6.

Base case de novo analysis

The base-case cost-effectiveness analysis reflects the NICE reference case.

Assumptions

All assumptions that were used to support the construction of the economic model are described in Table 5-24.

Table 5-24: List of assumptions used in the economic model

Area	Assumption	Justification
Population	The endpoints studied in the OPTiM trial are applicable to all patients independent of their BRAF status.	The results from the OPTiM trial did not suggest that the efficacy of T-VEC is dependent on BRAFv600 mutation status.
Comparator	Although the relevant comparators as defined in the final scope are ipilimumab, vemurafenib (BRAFv600 positive mutation) and dabrafenib (BRAFv600 positive mutation), the cost-effectiveness analysis presents results versus ipilimumab only.	These are treatments which are approved by NICE for use in the NHS in England and included in the final scope of this appraisal. The adjustment using the Korn model was deemed inappropriate, and consequently the results unreliable, for the BRAF-inhibitors. In addition, ipilimumab is deemed to be a key comparator given that it is an immunotherapy like T-VEC and is likely to be used in clinical practice to treat patients in the early stage disease whereas the BRAF inhibitors are likely to be reserved for severe patients who need a quick response.
Time horizon	30 years	This captures the lifetime time horizon (<5.72% of patients alive at this point) in line with the NICE reference case. The average age of patients in the model is 67 and a 30 year time horizon is long enough to reflect the difference in costs and outcomes between T-VEC and ipilimumab.
Treatment pathway	A three state model was used where patients are followed through three health states: • Non-progressive disease • Progressive disease • Death	Three state models have been used in previous melanoma appraisals and deemed acceptable by NICE.
Efficacy	It is plausible that T-VEC has a better chance of improving survival in its anticipated licensed population versus ipilimumab over time and at worst T-VEC is expected to be no less effective.	Given the issue of broken networks and the heterogeneity between OPTiM and the ipilimumab trials, the Korn model adjustments (modified Korn approach and the two-step Korn approach) were applied to estimate the survival for ipilimumab compared to T-VEC. Both

Area	Assumption	Justification
		cost and clinical outcomes are extrapolated beyond observed follow-up periods. For clinical outcomes, the methods used to perform this extrapolation are presented in Section 4.11. The use of AJCC registry and Office of National Statistics data after 4.58 years and 5.17 years for ipilimumab and T-VEC respectively assumes that there is no difference in the risk of death between T-VEC and ipilimumab after this point.
HRQoL	The quality of life of patients was captured by progression-based utilities through EQ-5D and was taken from the NICE melanoma appraisal TA321. The health state utility value for patients in the pre-progression disease state and post-progression disease state was summed by treatment arm over the model horizon.	Evaluation of HRQoL through EQ-5D using the validated, generic, choice-based EQ-5D is consistent with the NICE reference case.
Safety	The incidence of AEs from OPTiM trial was assumed to reflect that observed in clinical practice. The costs associated with AEs grade 3 and above with an incidence greater than 2% were included in the cost-effectiveness model.	Previous submissions in melanoma considered the inclusion of AEs grade 3 and above regardless of incidence. Given that the OPTiM trial reported only one AE for the T-VEC arm that was grade 3 and above and given that this AE is captured in the cost-effectiveness model, this assumption is conservative in favour of comparator ipilimumab.
Costs	Vial sharing is not allowed.	Vial sharing has not been accepted by NICE in previous submissions. The base case therefore assumes no vial sharing and the number of vials calculated and used in the model is based on whole vials and includes wastage.
	Palliative care assumes BSC for three months prior to death.	In TA319, palliative care assumed BSC for 3 months prior to death. This was assessed in sensitivity analysis.
Resource use	Resource use data was based on an Amgen costing study which estimated health resource use associated with the treatment of metastatic melanoma based on country-specific treatment pathways including the UK.	Resource use data based on the MELODY study has been used in previous melanoma appraisals. This was assessed in sensitivity analysis as an alternative source of data on resource use.

Source: Andtbacka 2015[79], NICE 2013[125], NICE TA 319[2], Johnston 2012[137]; Lorigan 2014[138]

AE, adverse event; AJCC, American Joint Committee on Cancer; BSC, best supportive care;

Area	Assumption	Justification
HRQoL, health-related quality of life; T-VEC, talimogene laherparepvec		

5.7 Base-case results

Base-case cost-effectiveness results

The results of the economic model for patients with non-visceral metastatic melanoma (stage IIIB/C and IVM1a), are presented below in Table 5-25.

Using the modified Korn adjustment, the estimated mean OS was 6.66 years for patients treated with T-VEC and 4.90 years for patients treated with ipilimumab. Patients treated with T-VEC accrued 4.91 QALYs compared with 3.57 QALYs among patients on ipilimumab.

Using the two-step Korn adjustment, the estimated mean overall survival was 6.66 years for patients treated with T-VEC and 6.16 years for patients treated with ipilimumab. Patients treated with T-VEC accrued 4.95 QALYs compared with 4.61 QALYs among patients treated with ipilimumab.

Base-case incremental cost effectiveness analysis results

There is robust RCT data for T-VEC in the non-visceral metastatic disease (stage IIIB-IVM1a) population that demonstrates a significant OS gain. However, there is a dearth of data for the comparators in this patient population and consequently the clinical issue of the presence and the magnitude of interaction with treatment effect for the comparators in the T-VEC patient population is unknown. There is therefore genuine uncertainty around the “true” estimate of ipilimumab efficacy in patients with non-visceral metastatic disease (stage IIIB-IVM1a). The modified Korn adjustment accounts only for prognostic variability and may not include any potential treatment interaction effect for ipilimumab. The two-step Korn adjustment, in contrast, bestows the full treatment interaction effect based on a small subgroup of patients. The efficacy of ipilimumab is likely to lie between these two approaches of adjustment using the Korn model. For this reason, both are presented as a base case to reflect both ends of the spectrum.

T-VEC is a cost-effective option when compared with ipilimumab at the usual ICER thresholds accepted by NICE. Table 5-25 below presents the base case incremental cost-effectiveness results for comparison of T-VEC and ipilimumab in patients with non-visceral metastatic disease. It should be noted that these results are based on the anticipated list price for T-VEC and the NHS list price ipilimumab. Ipilimumab is available with a confidential PAS by way of a simple discount to the NHS; however, there is a lack of publicly available information regarding the PAS for ipilimumab. A comparison of the ICERs in a range of simple discounts (from 0%-100%) to reflect the possible PAS for ipilimumab is presented in Table 5-26 below.

T-VEC resulted in 1.34 additional QALYs and an additional cost of [redacted] when using the modified Korn method. When using the two-step Korn method, T-VEC resulted in 0.35 additional QALYs with an additional cost of [redacted]. As shown by the base-case results, the modified Korn method and the two-step Korn method demonstrate that based on anticipated

list price, T-VEC is cost-effective when compared with ipilimumab based on NHS list price at the usual ICER thresholds accepted by NICE (Table 5-25).

In the analyses that used the modified Korn method and compared T-VEC with ipilimumab in a range of potential PAS discounts, the ICER remained below a threshold of £20,000 per QALY when a 35% discount was assumed [redacted]. The ICER remained below a threshold of £30,000 per QALY when a 55% discount was assumed [redacted]; Table 5-26).

In the analyses that used the two-step Korn method and compared T-VEC with ipilimumab in a range of potential PAS discounts, the ICER remained below a threshold of £20,000 per QALY when a 5% discount was assumed [redacted]. The ICER remained below a threshold of £30,000 per QALY when a 10% discount was assumed ([redacted]; Table 5-26).

Table 5-25: Base-case results (discounted, considering anticipated and current NHS list prices)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Modified Korn							
IPI	98,219	4.90	3.57	-	-	-	-
T-VEC	[redacted]	6.66	4.91	[redacted]	1.76	1.34	[redacted]
Two-Step Korn							
IPI	96,035	6.16	4.61	-	-	-	-
T-VEC	[redacted]	6.66	4.95	[redacted]	0.50	0.35	[redacted]
ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; LYG, life years gained; QALYs, quality-adjusted life years; T-VEC, talimogene laherparepvec							

Table 5-26: Comparison of ICERs assuming a range of potential discounts for ipilimumab with anticipated list price for T-VEC

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
0%	[redacted]	[redacted]
5%	[redacted]	[redacted]
10%	[redacted]	[redacted]
15%	[redacted]	[redacted]
20%	[redacted]	[redacted]
25%	[redacted]	[redacted]
30%	[redacted]	[redacted]
35%	[redacted]	[redacted]
40%	[redacted]	[redacted]
45%	[redacted]	[redacted]
50%	[redacted]	[redacted]
55%	[redacted]	[redacted]
60%	[redacted]	[redacted]

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
65%	[redacted]	[redacted]
70%	[redacted]	[redacted]
75%	[redacted]	[redacted]
80%	[redacted]	[redacted]
85%	[redacted]	[redacted]
90%	[redacted]	[redacted]
95%	[redacted]	[redacted]
100%	[redacted]	[redacted]

Clinical outcomes from the model

A comparison of the clinical outputs estimated by the model and those obtained from the OPTiM clinical trial and the ipilimumab clinical trials is presented in Table 5-27. The comparison shows that the results for T-VEC estimated by the economic model are similar to those reported in the OPTiM trial. The median OS for T-VEC was estimated to be 4.01 years. This was 0.10 years higher than the median OS observed in the OPTiM trial (3.91 years). The restricted mean OS at 5 years was estimated to be 3.07 years. This was 0.21 years lower than the restricted mean OS observed in the OPTiM trial (3.28 years). The median PFS was estimated to be 1.09 years and was in line with the median PFS observed in the OPTiM trial. The percentage of patients with PFS at 0.5 years was estimated to be 65.97%. This was 2.39% lower than the value observed in the OPTiM trial. The similarity of the results suggests that the short-term and long-term outcomes from the model are valid for T-VEC.

The Korn methodology (modified Korn adjustment and two-step Korn adjustment were applied to estimate the survival of ipilimumab in the anticipated T-VEC licensed population. Given that the adjustment shifted upwards the survival curves for ipilimumab in this patient population with non-visceral metastatic disease, the comparison of the outputs estimated by the model based on the Korn methods of adjustment and the outputs from the clinical trials for ipilimumab which studied mostly patients with later stage metastatic disease are different. Using the modified Korn method, the model estimated the median OS for ipilimumab to be 1.71 years. This was 0.79 years and 0.86 years higher than the median OS observed in the first-line and second-line ipilimumab trials, respectively. The restricted mean OS at 5 years was estimated to be 2.37 years. This was 0.7 years and 0.8 years higher than the ipilimumab trials. The median PFS for ipilimumab estimated by the model using the modified Korn method was 0.56 years. This was 0.33 years higher than the median OS observed in both the first-line and second-line ipilimumab trials. The percentage of patients with PFS at 0.5 years was estimated to be 52.75% using the modified Korn method. This was 20.9% and 31.0% higher than the values observed in the first-line and second-line ipilimumab trials, respectively.

Using the two-step Korn method, the model estimated the median OS for ipilimumab to be 3.87 years. This was 3.09 years and 3.16 years higher than the median OS observed in the first-line and second-line ipilimumab trials, respectively. The restricted mean OS at 5 years

was estimated to be 2.91 years. This was 1.24 years and 1.34 years higher than the ipilimumab trials. The median PFS for ipilimumab estimated by the model using the two-step Korn method was 1.11 years. This was 0.88 years higher than the median OS observed in both the first-line and second-line ipilimumab trials. The percentage of patients with PFS at 0.5 years was estimated to be 66.83% using the two-step Korn method. This was 34.98% and 45.08% higher than the values observed in the first-line and second-line ipilimumab trials, respectively.

Table 5-27: Summary of model results compared with clinical data

	Model Results				Clinical Trial Results			
	Modified Korn		Two-Step Korn		T-VEC (OPTiM)	Ipilimumab		Ipilimumab
						CA184-024	MDX010-20	CA184-024 and MDX010-20
Outcome	**T-VEC**	**Ipilimumab (pooled)***	**T-VEC**	**Ipilimumab (pooled)***	**Previously Treated and Untreated**	**Previously Untreated**	**Previously Treated**	**Pooled* (previously untreated and treated)**
Median OS (years)	4.01	1.71	4.01	3.87	3.91	0.92	0.84	0.90
Restricted mean OS (5 years)	3.07	2.37	3.07	2.91	3.28	1.67	1.57	1.62
Median PFS (years)	1.09	0.56	1.09	1.11	1.09	0.23	0.23	0.23
% patients with PFS at 0.5 years	65.97%	52.75%	65.97%	66.83%	68.36%	31.85%	21.75%	28.23%
OS, overall survival; PFS, progression free survival; T-VEC, talimogene laherparepvec ; 8pooled using modified Mantel-Haenszel method (Appendix 1.10)								

Proportion of the cohort in the health state over time (Markov trace) for each state

Figure 5-30 and Figure 5-31 illustrate how patients move through the model health states over time when treated with T-VEC and ipilimumab, respectively, using the modified Korn method. Similarly, Figure 5-32 and Figure 5-33 illustrate how patients move through the model health states over time when treated with T-VEC and ipilimumab, respectively, using the two-step Korn method.

Figure 5-30: Markov trace for T-VEC: modified Korn

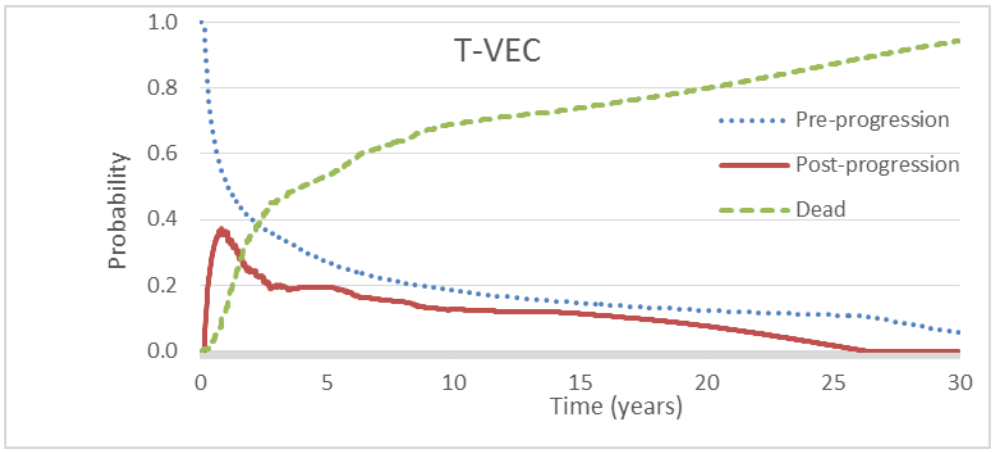


Figure 5-31: Markov trace for ipilimumab: modified Korn

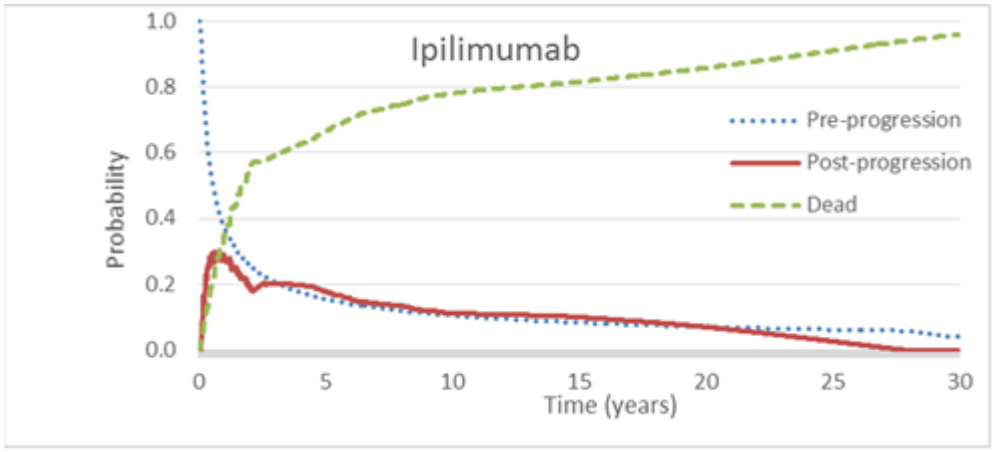


Figure 5-32: Markov trace for T-VEC: two-step Korn

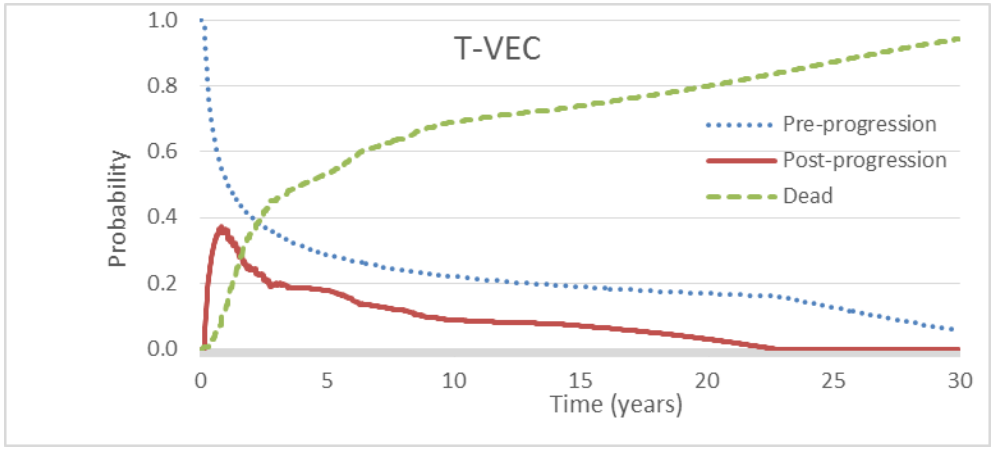


Figure 5-33: Markov trace for ipilimumab: two-step Korn

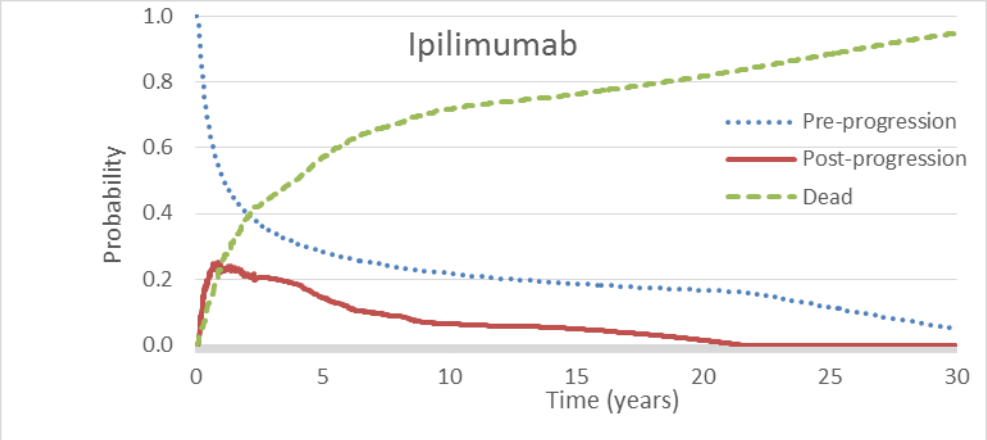
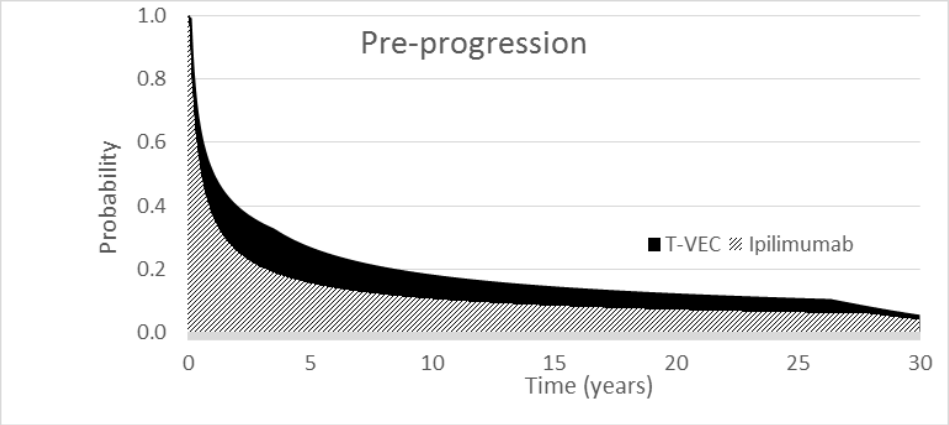


Figure 5-34 shows the proportion of patients who are in the pre-progression health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. When using the modified Korn method, the results show patients treated with T-VEC spend longer in the pre-progression health state than do patients treated with ipilimumab (Figure 5-34a). This is due to the improved PFS associated with T-VEC as seen in the OPTiM clinical trial Table 5-27. However, this effect is less pronounced when the two-step Korn method is used (Figure 5-34b); the median PFS for T-VEC and ipilimumab are almost identical. This is due to the significant adjustment ascribed to ipilimumab with the two-step Korn adjustment, which increases its PFS almost fivefold compared to that observed in clinical trials (Table 5-27).

Figure 5-34: Markov trace for the pre-progression health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment

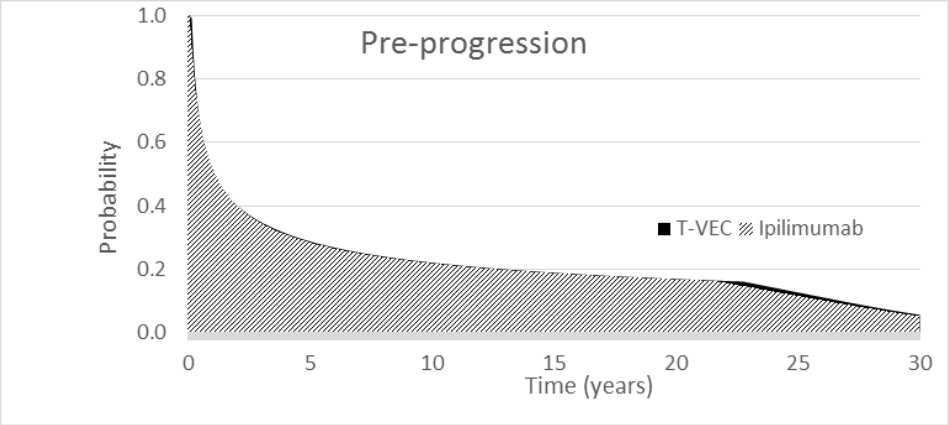


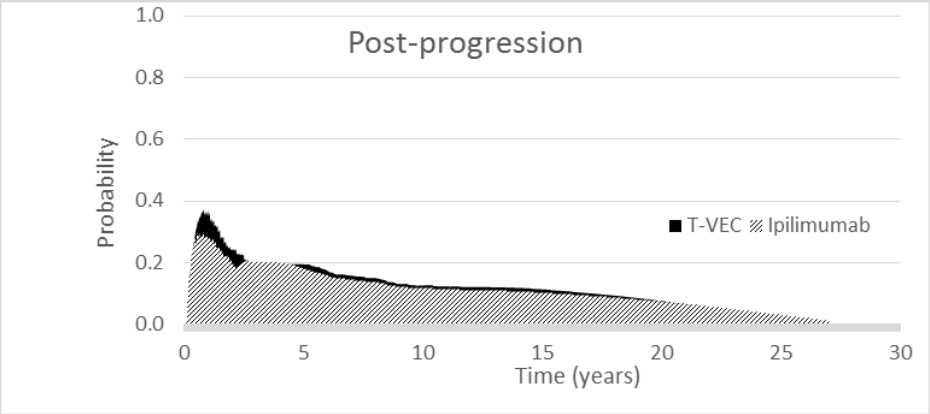
Figure 5-35 shows the proportion of patients who are in the post-progression health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. When using the modified Korn method, the results show that more patients treated with T-VEC remain in the post-progression health state than do patients treated with ipilimumab (Figure 5-35a and Figure 5-35b). This is driven by the improved OS associated with T-VEC (Table 5-27).

The same is true when using the two-step Korn method. Overall, more patients treated with T-VEC remain in the post-progression health state. However, the survival gain for T-VEC is less pronounced given that this method ascribed the full interaction effect for ipilimumab, significantly boosting the OS for ipilimumab in a population aligned with the anticipated T-VEC license (Table 5-27).

The proportion of patients in the post-progression health state is higher for ipilimumab between 2.7 years and 3.9 years using both the modified Korn and two-step Korn methods. This reflects the period where the modified Korn adjusted and the two-step Korn adjusted Kapan-Meier OS is higher for ipilimumab compared with T-VEC.

Figure 5-35: Markov trace for the post-progression health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment

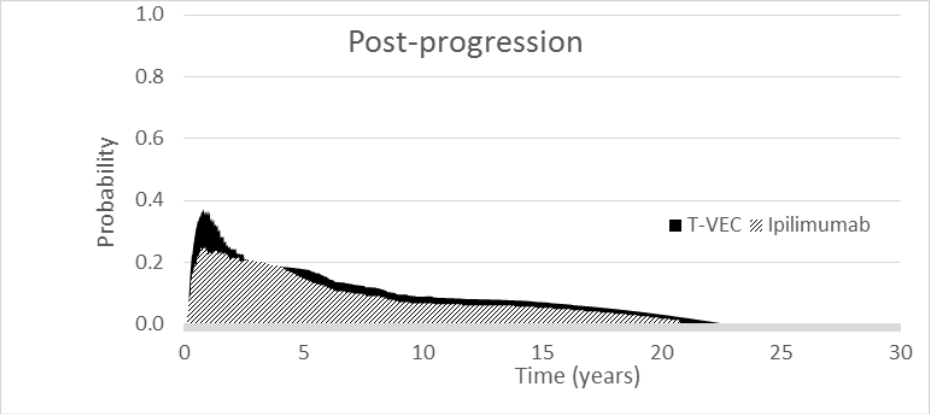
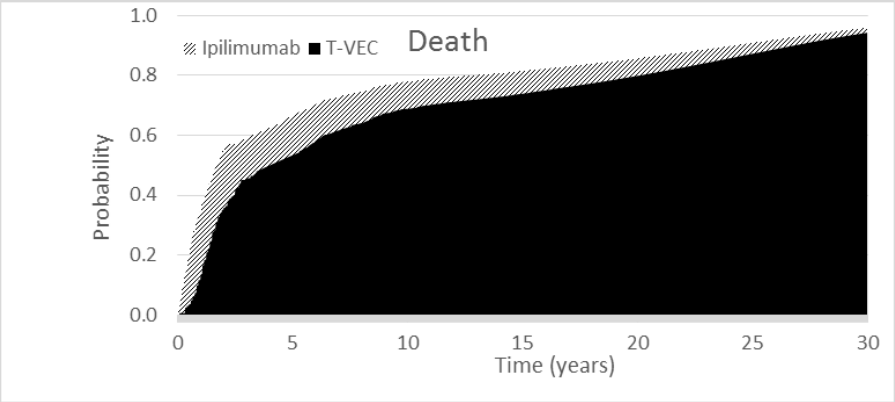


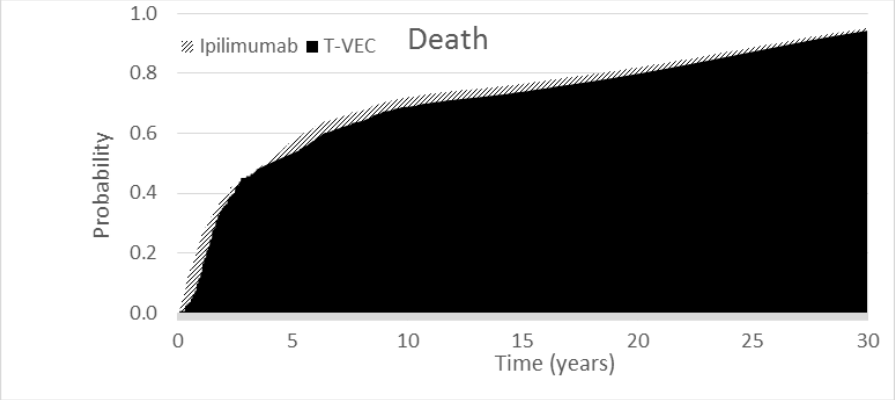
Figure 5-36 shows the proportion of patients who are in the death health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. The figure demonstrates the improved OS for patients treated with T-VEC.

Figure 5-36: Markov trace for the death health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment



Details of how the model assumes QALYs accrued over time

Figure 5-37, Figure 5-38, and Figure 5-39 shows how the costs, QALYs, and life-years accumulate over time, respectively, for patients treated with T-VEC and ipilimumab using the modified Korn and two-step Korn methods. In the base case, QALYs are accrued according to progression status over time as previously reported.

Total costs initially are similar for T-VEC and ipilimumab, but T-VEC becomes more expensive after approximately 1.72 years using the modified Korn approach and after approximately 0.96 years when using the two-step Korn approach (Figure 5-37). This increase is driven by the increased cost of BSC and/or palliative care accrued by patients who receive T-VEC live longer and therefore remain in the progressive disease health state for longer than patients who receive ipilimumab. It should be noted that drug and administration costs are not included in the total costs given they are not calculated in a time-dependent manner.

Figure 5-38 and Figure 5-39 demonstrate that QALYs and life-years gained are higher for patients treated with T-VEC than for patients treated with ipilimumab. This is driven by improved PFS and OS associated with T-VEC. The incremental QALY gain and life-year gain is higher when using the modified Korn approach because of the lower PFS and OS

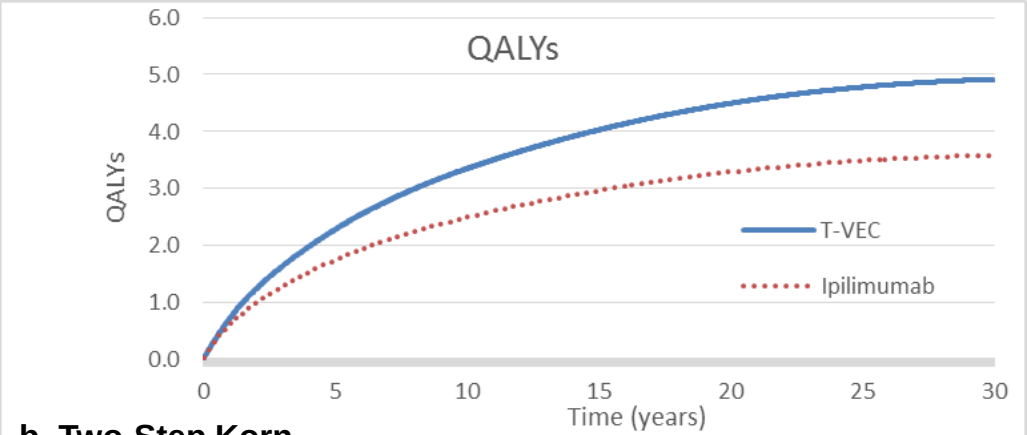
estimates for ipilimumab. The improved QALY gain and life-year gain accrued for T-VEC versus ipilimumab diminishes over time as fewer patients remain alive in the model and the OS curves converge.

Figure 5-37: Cumulative costs over time for patients treated with either T-VEC or ipilimumab: modified Korn (a) and two-step Korn (b)

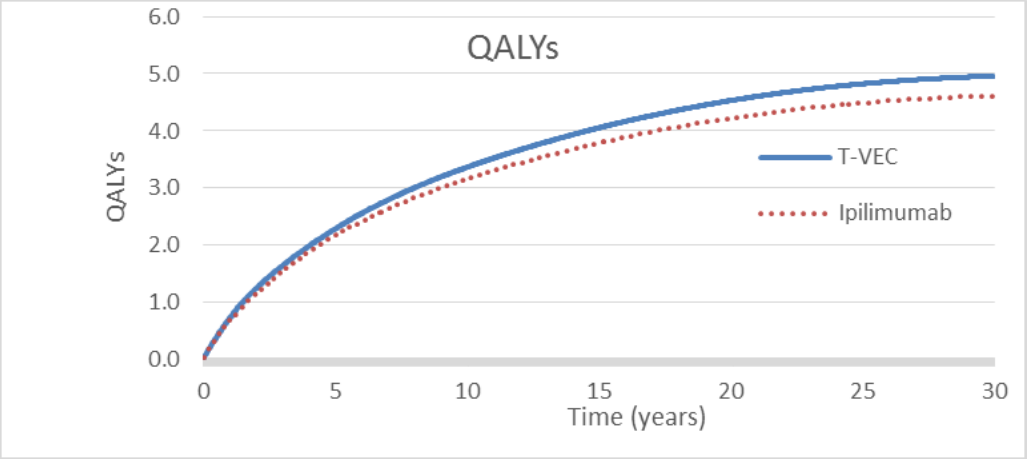
* Drug and administration costs are not included in the total beause they are not calculated in a time-dependent manner.

Figure 5-38: Cumulative QALYs over time for patients treated with either T-VEC or ipilimumab: modified Korn (a) and two-step Korn (b)

a. Modified Korn



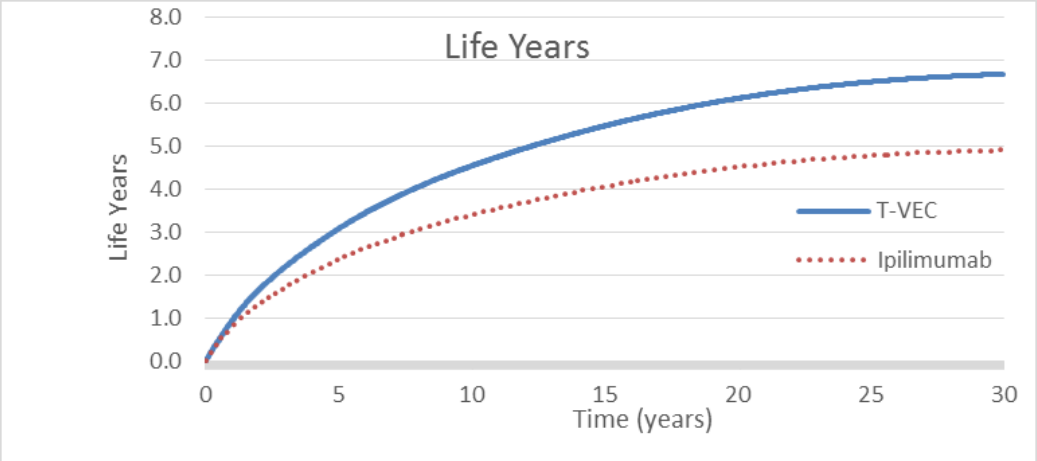
b. Two-Step Korn



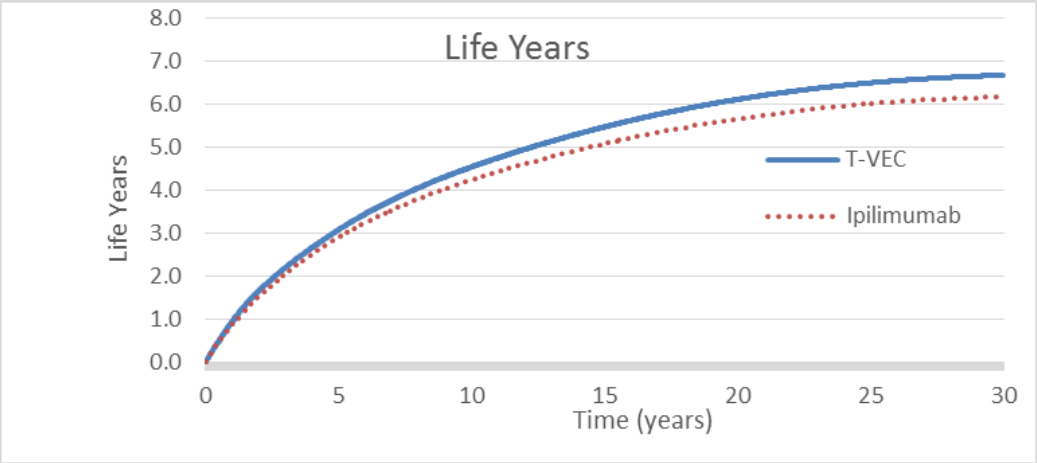
QALY, quality-adjusted life-year

Figure 5-39: Cumulative LYs over time for patients treated with either T-VEC or ipilimumab: modified Korn and two-step Korn

a. Modified Korn



b. Two-Step Korn



Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 5-28 illustrates the QALY gain by health state using the modified Korn and two-step Korn methods. Compared with patients treated with ipilimumab, in general, patients treated with T-VEC spend a longer time in both the pre- and post-progression health states; this is the case even when using the two-step Korn adjustment (worst case scenario for T-VEC) which ascribes the full interaction effect for ipilimumab in the T-VEC proposed licensed population. It is noteworthy that the increment is much larger for the pre-progression health state using the modified Korn method, whereas, the increment is larger for the post-progression health state using the two-step Korn method.

Table 5-28: Summary of QALY gain by health state

Health state	QALY: T-VEC	QALY: Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Pre-progression	3.25	2.06	1.19	1.19	89.13%
Post-progression	1.66	1.51	0.15	0.15	10.87%
Total	4.91	3.57	1.34	1.34	100%
Two-step Korn					
Pre-progression	3.61	3.55	0.06	0.06	16.80%
Post-progression	1.34	1.05	0.29	0.29	83.20%
Total	4.95	4.61	0.35	0.35	100%

QALY, quality-adjusted life year; T-VEC, talimogene laherparepvec

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 5-29 illustrates the disaggregated costs using the modified Korn and two-step Korn methods. Over a patient's lifetime, treatment with ipilimumab is expected to cost approximately £98,219. By comparison, treatment with T-VEC is expected to cost approximately [redacted] when the modified Korn adjustment method is used. When the two-step Korn adjustment method is used, ipilimumab and T-VEC are expected to cost approximately £96,035 and [redacted], respectively, over a patient's lifetime.

Table 5-29: Summary of costs and predicted resource use by health state

Health state	T-VEC	Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Pre-progression	[redacted]	£80,257	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	£17,963	[redacted]	[redacted]	[redacted]
Total	[redacted]	£98,219	[redacted]	[redacted]	[redacted]
Two-step Korn					
Pre-progression	[redacted]	£81,707	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	£14,328	[redacted]	[redacted]	[redacted]
Total	[redacted]	£96,035	[redacted]	[redacted]	[redacted]

T-VEC, talimogene laherparepvec

Adapted from: Pharmaceutical Benefits Advisory Committee (2008) guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 5-30 illustrates the predicted resource use by category of cost. T-VEC is associated with higher administration costs given the increased number of administrations compared to ipilimumab. In contrast, T-VEC with its favourable tolerability profile is associated with a lower cost of managing AEs compared to ipilimumab using both the modified Korn and two-step Korn methods.

Table 5-30: Summary of predicted resource use by category of cost

Item	T-VEC	Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.73%
Resource use	£35,561	£28,752	£6,810	£7,756	38.43%
AEs	£3	£118	–£115	£115	0.57%
Total	[redacted]	£98,219	[redacted]	[redacted]	[redacted]
Two-step Korn					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.43%
Resource use	£34,419	£26,567	£7,852	£8,092	39.44%
AEs	£3	£118	–£115	£115	0.56%
Total	[redacted]	£96,035	[redacted]	[redacted]	[redacted]

AE, adverse event; T-VEC, talimogene laherparepvec

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 1.6 (List of model parameters).

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 5-31. These results are based on the anticipated list price for T-VEC and NHS list price for ipilimumab. In the modified Korn method, T-VEC is associated with an incremental cost of [redacted] and 1.24 incremental QALYs compared with ipilimumab. The ICER for the modified Korn analysis of [redacted] per QALY gained based on the probabilistic analysis remains close to the deterministic ICER of [redacted] per QALY gained

For the two-step Korn analysis, T-VEC is associated with an incremental cost of [redacted] and 0.24 incremental QALYs. The ICER for the two-step Korn analysis is [redacted] per QALY gained.

Table 5-31: Incremental cost-effectiveness results based on PSA

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs
Modified Korn					
T-VEC	[redacted]	4.79 (4.03-5.43)	[redacted]	1.24 (0.57-1.69)	[redacted]
Ipilimumab	£99,129 (£87,286-£112,458)	3.56 (3.11-3.97)			
Two-step Korn					
T-VEC	[redacted]	4.82 (4.06-5.39)	[redacted]	0.24 (-0.46-0.73)	[redacted]
Ipilimumab	£103,541 (£91,357-£116,535)	4.58 (4.19-4.95)			

The scatterplot of PSA iterations in Figure 5-40 and Figure 5-41 shows that there is little overlap in terms of the total costs and total QALYs for T-VEC and ipilimumab when using the modified Korn method and a considerable overlap when using the two-step Korn method. However, even in the worst case scenario (for T-VEC) using the two-step Korn method of estimating survival for ipilimumab in the anticipated T-VEC licensed population, the costs for T-VEC are generally slightly lower and the number of QALYs gained is generally slightly higher.

The cost-effectiveness acceptability curves show that when using the modified Korn adjustment (Figure 5-42) there is an approximately 98.39% chance of T-VEC being cost-effective when compared to ipilimumab at the £20,000 per QALY threshold (and 99.70% at a threshold of £30,000). When using the two-step Korn adjustment, which ascribes the best possible treatment effect to ipilimumab in the proposed T-VEC licensed population, the cost-effectiveness acceptability curve in Figure 5-43 shows that there is an approximately 80.02% chance of T-VEC being cost-effective when compared to ipilimumab at the £20,000 per QALY threshold (and 81.83% at a threshold of £30,000).

Figure 5-40: Scatterplot of PSA results (1,000 simulations; results discounted, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively) Modified Korn

Figure 5-41: Scatterplot of PSA results (1,000 simulations; results discounted, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively) Two-Step Korn

Figure 5-42: Cost-effectiveness acceptability curve (results discounted, with with anticipated and current NHS list prices for T-VEC and ipilimumab respectively): Modified Korn

Figure 5-43: Cost-effectiveness acceptability curve (results discounted, with with anticipated and current NHS list prices for T-VEC and ipilimumab respectively): Two-Step Korn

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted where modelling assumptions are changed one at a time for key variables. The following variables were increased and decreased by 20%:

- Duration of treatment
- Response rates
- Administration costs
- Discount rates
- Health state utility values

- Costs of terminal care

The results of the deterministic sensitivity analyses for the comparisons with ipilimumab are presented in Figure 5-44. These are presented with the anticipated and current NHS list prices for both T-VEC and ipilimumab respectively. Across both approaches (modified Korn method and two-step Korn method), the ICER was most sensitive to the duration of treatment for both T-VEC and ipilimumab. The rest of the variables had a minor impact on the estimated ICER.

Figure 5-44: Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively)

a. Using Modified Korn Adjustment

b. Using Two-Step Korn Adjustment

Scenario analysis

In addition to conducting probabilistic and deterministic sensitivity analyses, alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions.

The following scenarios were evaluated:

- Varying the time horizon of the model: 10 years, 20 years and 25 years
- Varying the modelling approach for T-VEC dosing:
    - Include accelerated dosing and extension phase
    - Exclude accelerated dosing and extension phase
- Varying the modelling approach for IPI dosing
- Using alternative sources of utility estimates:
    - Beusterien study
    - TA 268
    - Amgen time trade study
- Applying alternative parametric curve fits:
    - Use log-normal and Weibull distributions as parametric curve fits for OS
    - Use log-normal and log-logistic distributions as parametric curve fits for PFS
- Applying alternative approach to modelling survival:
    - Use 2-part curve fit (Kaplan Meier+Regression) to model OS
    - Do not adjust long-term T-VEC PFS
- Varying resource use assumptions in terminal care:
    - TA319
- Varying resource use assumptions in routine treatment for non-progressive disease:
    - Costs of routine treatment with CR assumed to be zero for both T-VEC and IPI
    - Costs of routine treatment with CR, PR, SD, and PD reduced by 20%
    - Costs of routine treatment with CR, PR, SD, and PD increased by 20%

Table 5-32 reports the results of the scenario analyses. The scenario analysis showed that the cost-effectiveness of T-VEC is robust to the majority of potential sources of uncertainty. T-VEC was dominant (associated with lower costs and higher QALYs) for a number of the scenario analyses and remained cost-effective ([redacted] using the two-step Korn method) even in the scenario where a conservative dosing approach was evaluated (including both accelerated dosing and extension phase dosing).

Table 5-32: Results of the scenario analyses

Parameter	Base Case assumptions	Sensitivity Analysis	Modified Korn ICER		Two-Step Korn ICER	
			£/QALY	£/LYG	£/QALY	£/LYG
Base case result:			[redacted]	[redacted]	[redacted]	[redacted]
Varying the time horizon						
Time horizon	30 years	10 years	Dominant	Dominant	Dominant	Dominant
		20 years	[redacted]	[redacted]	[redacted]	[redacted]
		25 years	[redacted]	[redacted]	[redacted]	[redacted]
Varying the modelling approach for T-VEC dosing						
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Dominant	Dominant	Dominant	Dominant
Varying the modelling approach for IPI dosing						

IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	Dominant	Dominant	Dominant	Dominant
Varying the approach to modelling utilities						
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al.	[redacted]	[redacted]	[redacted]	[redacted]
		IPI 1 L (TA268)	[redacted]	[redacted]	[redacted]	[redacted]
		Amgen TTO study	[redacted]	[redacted]	[redacted]	[redacted]
Alternative parametric curve fits						
OS	Exponential	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS	Generalised gamma	Log-normal	[redacted]	[redacted]	Dominant	Dominant
		Log-logistic	[redacted]	[redacted]	Dominant	Dominant
Alternative approach to modelling survival						
OS	3-part curve fit	2-part curve fit	[redacted]	[redacted]	[redacted]	[redacted]
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	[redacted]	[redacted]	[redacted]
Varying resource use assumptions in terminal care						
Cost of terminal care	Amgen resource use study	TA319*	[redacted]	[redacted]	[redacted]	[redacted]
Varying resource use assumptions in routine treatment for non-progressive disease						
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR assumed to be zero for both T-VEC and IPI	[redacted]	[redacted]	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	[redacted]	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	[redacted]	[redacted]	[redacted]

BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; LYG, life-year gained; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; QALY, quality-adjusted life-year; SPC, summary of product characteristics; T-VEC, talimogene laherparepvec

Summary of sensitivity analyses results

For the modified Korn adjustment, the probability of T-VEC being cost effective at a £20,000 per QALY threshold is 98.39% when compared to ipilimumab. Even in the worst case scenario for T-VEC using the two-step Korn adjustment, the probability of T-VEC being cost effective at a £20,000 per QALY threshold is 80.02% compared to ipilimumab.

One-way sensitivity analysis demonstrated that the duration of treatment for both ipilimumab and T-VEC had the greatest impact on the ICER for both the modified Korn method and the two-step Korn method.

Scenario analysis showed that the cost-effectiveness of T-VEC is robust to the majority of potential sources of uncertainty. The least favourable ICER, of [redacted] per QALY gained, was produced when T-VEC dosing included accelerated dosing and extension phase dosing using the two-step Korn method of adjustment.

5.9 Subgroup analysis

No subgroup analyses were considered in the cost-effectiveness analysis.

5.10 Validation

Validation of de novo cost-effectiveness analysis

The general model structure is consistent with metastatic melanoma models developed by comparator manufacturers that have been accepted by NICE. As outlined in Section 6.3, these elements were validated by key opinion leaders practising in the UK. The input of these clinicians and health economic experts has been used to inform the methods for survival analyses, dosing and application of adverse events. The opinions provided by these experts were also used in order to determine the model base case in terms of survival analysis using the modified Korn adjustment and the two-step Korn adjutsment.

Quality-control procedures for verification of input data and coding were performed by staff not involved in the model development. A checklist was used to ensure that the model generated accurate results and that these results are consistent with input data and robust to extreme values. The checks are documented in Appendix 1.9

As described in Table 5-27, the model predicted outcomes, both short and long term, for T-VEC in line with that observed in the pivotal clinical trial OPTiM. The Korn methodology (modified Korn adjustment and two-step Korn adjustment) was applied to estimate the survival of ipilimumab in the anticipated T-VEC licensed population. Given that the adjustment shifted upwards the survival curves for ipilimumab in this patient population with non-visceral metastatic disease, the comparison of the outputs estimated by the model based on the Korn methods of adjustment and the outputs from the clinical trials for ipilimumab which studied mostly patients with later stage metastatic disease are different.

5.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

No study assessing the cost-effectiveness of T-VEC was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

It was also not possible to compare the results of this submission to previous submissions given that the patient population assessed in this appraisal, non-visceral metastatic melanoma (Stage IIIB, IIIC and IVM1a), is different to the previous appraisals for melanoma which studied mostly patients in later stage metastatic disease.

Relevance of the economic evaluation for all patient groups

The target population included in the economic evaluation was consistent with the population eligible for T-VEC as per the proposed license. There is robust RCT data for T-VEC showing a clinically significant OS gain in its anticipated licensed population, i.e. the non-visceral metastatic disease (stage IIIB-IVM1a) population and consequently the evidence considered for T-VEC was in line with its proposed license.

Given the issue of broken networks and the heterogeneity of patient populations between T-VEC and comparator trials, it was not feasible to conduct an NMA. In addition, there is a dearth of data for the comparators in this patient population and consequently the clinical issue of the presence and the magnitude of interaction with treatment effect for the comparators in the T-VEC patient population are unknown. As there was no data for ipilimumab in the anticipated T-VEC licensed population (non-visceral metastatic melanoma, Stage IIIB/C, IVM1a), two alternative approaches using the modified Korn method and the two-step Korn method was used to estimate the survival for ipilimumab. The base case presents both approaches, the modified Korn method which assumes the absence of an interaction effect for ipilimumab in the anticipated T-VEC licensed population (best case) and the two-step Korn method which assumes the full interaction effect for ipilimumab based on uncertain clinical evidence (worst case). The likely ICER is expected to lie somewhere between the best and the worst case approaches.

Generalisability of the analysis to the clinical practice in England

The population included in the OPTiM trial, the main source of clinical evidence for T-VEC considered in the economic model, was generally comparable with the UK population. In terms of the treatment pathway, based on advice from clinical experts, patients with non-visceral metastatic disease are likely to receive an immunotherapy such as ipilimumab as first-line treatment, while BRAF inhibitors would be reserved patients with severe disease needing a rapid response. Therefore, the comparison of T-VEC in line with the expected license, versus ipilimumab is highly relevant to clinical practice.

Strengths and weaknesses of the evaluation

This is the first appraisal to evaluate the efficacy of a treatment for metastatic melanoma in the earlier stage of disease (i.e. non-visceral metastatic disease). While there is robust data for T-VEC it its proposed licensed population, there is a dearth of data for the comparators including ipilimumab. As such, different approaches to estimating survival for ipilimumab was used, one excluding the presence of any interaction with treatment effect (modified Korn

model) and another assuming the full interaction effect (two-step Korn model) It may be deemed that the “true” estimate of ipilimumab survival in non-visceral metastatic disease (stage IIIB-IVM1a), lies between the modified Korn adjustment which accounts only for prognostic variability and may not include any potential treatment interaction effect for ipilimumab and the two-step Korn adjustment which bestows the full treatment interaction effect based on a small subgroup of patients.

The model structure is based on overall survival and assumes that overall survival is a product of responses to both first and subsequent lines of treatment, as experienced in the RCTs. This structure was chosen because of the consistency between the costs and health outcomes. Although the use of subsequent therapies was balanced across treatment arms within the OPTiM trial and within the ipilimumab trial, the relative impact of subsequent therapies for T-VEC compared to ipilimumab is unclear and may be seen as a weakness of the evaluation.

Further analyses

There is genuine uncertainty around this important clinical issue of the presence of treatment interaction effect and the magnitude of the interaction effect for ipilimumab. The proposed confidential discount for T-VEC is a response to the uncertainties around this important clinical issue and mitigates any risk to the NHS. These uncertainties relate more to limitations of the evidence base of other comparators in T-VEC’s expected indication.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

Not applicable.

6.2 Number of people eligible for treatment in England

The patient population eligible for treatment with T-VEC has been estimated using the assumptions described in Table 6-1.

Table 6-1: With Stage IIIB, IIIC, IVM1a and unresectable disease - Assumptions

Assumption	Value		Source
Incident malignant melanoma population in 2011	13,348		Cancer Research UK incident malignant melanoma cases in 2011[23]
% Increase in incidence per annum	3.5%		NICE TA268[57]
Estimate of incident malignant melanoma population in 2015 (all stages	15,317		Calculated
Proportions of patients with stage IIIB – IVM1a disease	Stage IIIB/C	Stage IVM1a	Proportion of incident malignant melanoma patients with stage IIIB, IIIC, and IVM1a[22] disease
	3.6% (IIIB), 1.9% (IIIC)	3.8%	
Proportions of patients with injectable disease	73%	73%	Proportion of patients with lesions that are suitable for injection[80]
Proportions of patients diagnosed with metastatic or unresectable melanoma in whom chemotherapy/active treatment is suitable	70%	70%	NICE TA268[57]

The incident malignant melanoma population in England in 2011 was used to estimate the number of expected cases in 2015 by assuming an annual increase in incidence of 3.5%[57].

The number of patients eligible for treatment with T-VEC within its anticipated license (unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease) was subsequently estimated from the proportions of patients with stage IIIB – IVM1a disease with injectable lesions and suitability for active treatment. It is

estimated that 728 patients will be eligible for treatment in the first year, and the number of eligible patients from year 1 to year 5 (2015 – 2019) is presented in Table 6-2.

Table 6-2: Estimated eligible adult population with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease

Assumption	Year 1	Year 2	Year 3	Year 4	Year 5
	2015	2016	2017	2018	2019
Estimate of incident melanoma population in 2015 (all stages)	15,317	15,853	16,408	16,982	17,577
Proportions of patients with stage IIIB – IVM1a disease	1,424	1,474	1,526	1,579	1,635
Proportions of patients with injectable disease	1,040	1,076	1,114	1,153	1,193
Proportions of patients diagnosed with metastatic or unresectable melanoma in whom chemotherapy/active treatment is suitable	728	753	780	807	835
Eligible patients	728	753	780	807	835

6.3 Assumptions made about current treatment options and uptake of technologies

The main assumptions for estimating the number of patients eligible for treatment with T-VEC are:

- All patients are tested for BRAF V600 mutation status[57]
- 0% are treated through clinical trials[57]
- 3.5% incidence change rates per year[2]

As defined in the decision problem of this appraisal, the current treatment options in the patient population for which T-VEC is indicated are ipilimumab (NICE TA268[57], NICE TA319[2]), vemurafenib (NICE TA269[58]) and dabrafenib (NICE TA321[1]). All of these treatments have been recommended by NICE within their licensed indications as treatment options for the broader population of advanced (unresectable or metastatic) melanoma, however as described in Section 3.3, we consider ipilimumab to be the primary comparator in this appraisal.

It is noteworthy that although pembrolizumab is not defined as a relevant comparator in the scope of this appraisal, it is also likely to be a relevant treatment option in the patient population that T-VEC is indicated and as a conservative measure we have assumed a lower market share for T-VEC (Section 6.4) given the expected increase in the market share of pembrollizumab from ipilimumab.

6.4 Assumptions that were made about market share in England

The estimated market shares for T-VEC and the comparators defined in the scope of this appraisal are presented in Table 6-3 and it is assumed that:

- 48% of patients are BRAF V600 mutation positive[145] and 52% are BRAF V600 mutation negative
- T-VEC is used in both the BRAF V600 wild-type and BRAF V600 mutated populations
- Ipilimumab is used in both the BRAF V600 wild-type and BRAF V600 mutated populations
- Dabrafenib comprises nearly two-thirds of BRAF inhibitor use[80]
- The market shares above are applicable to the patient population with BRAF V600 positive mutation (48%) and BRAF wild type (52%)
- Pembrolizumab is not included since it is not a relevant comparator in this appraisal

It is assumed that the current market share for ipilimumab, vemurafenib and dabrafenib is 60%, 25% and 15% respectively, and that the uptake of T-VEC will increase over time as an alternative to the current treatments options. The market share assumptions for the BRAF inhibitors are based on European market research data[80] and the estimated market share for T-VEC is from Amgen internal forecasting. The absolute market shares and estimated number of patients eligible for treatment with T-VEC and the relevant comparators are summarised in Table 6-3 and Table 6-4 respectively.

Table 6-3: Estimated absolute market share of melanoma therapies in the T-VEC eligible patient population

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Current	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proposed	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		T-VEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6-4: Estimated numbers of patients eligible for treatment in the T-VEC eligible patient population

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Current	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Proposed	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		T-VEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Additional significant costs associated with treatment

Technology costs and other significant costs associated with administration of T-VEC are described in Section 5.3 to Section 5.6. The costs of monitoring have been included in addition to drug acquisition costs.

6.6 Unit costs

The costs considered in the budget impact analysis were derived from the economic model, as reported in Section 5.5 and includes:

- Acquisition costs
- Administration costs
- Adverse events costs
- Routine care costs
- Best supportive care costs

Given that ipilimumab is assumed to be the primary comparator in this submission, as a conservative measure, it was assumed that there will be no the impact of T-VEC on the BRAF inhibitors, and thus the costs of dabrafenib and vemurafenib have not been considered in the budget impact analysis.

6.7 Estimates of resource savings

The differential costs considered, both budget impact and budget savings, are incorporated as the incremental costs as calculated in the economic model.

6.8 Estimated budget impact on the NHS in England

The annual budget impact for the years 2015 to 2019 is provided in Table 6-5. As described in Section 6.7 the estimated budget impact includes the costs associated with drug acquisition and monitoring.

The introduction of T-VEC is anticipated to have a budget impact of [redacted] in 2015 and [redacted] in 2019 in adult patients with unresectable melanoma that is regionally or distantly metastatic with no visceral disease.

Table 6-5: Estimated budget impact over 5 years

Scenario	Costs	Year				
		Year 1	Year 2	Year 3	Year 4	Year 5
		2015	2016	2017	2018	2019

Scenario	Costs	Year				
		Year 1	Year 2	Year 3	Year 4	Year 5
		2015	2016	2017	2018	2019
Current	**Ipilimumab**					
	Drug costs*(£)	29,922,552	30,969,841	32,053,785	33,175,668	34,336,816
	Drug administration costs(£)	484,570	501,529	519,083	537,251	556,055
	AE costs (£)	51,973	53,792	55,675	57,623	59,640
	Non-progressive disease costs (routine care) (£)	1,071,784	1,109,296	1,148,122	1,188,306	1,229,897
	BSC costs(£)	941,878	974,844	1,008,963	1,044,277	1,080,827
	Total costs (£)	**32,472,756**	**33,609,303**	**34,785,628**	**36,003,125**	**37,263,235**
Future	**Ipilimumab**					
	Drug costs*(£)	28,426,424	21,162,725	18,698,042	19,352,473	20,029,810
	Drug administration costs(£)	460,341	342,712	302,798	313,396	324,365
	AE costs (£)	49,374	36,758	32,477	33,613	34,790
	Non-progressive disease costs (routine care) (£)	1,018,195	758,019	669,738	693,178	717,440
	BSC costs(£)	894,784	666,143	588,562	609,162	630,482
	Total costs (£)	**30,865,580**	**22,978,612**	**20,302,445**	**21,013,030**	**21,748,486**
	T-VEC					
	Drug costs*(£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Drug administration costs(£)	113,528	744,174	1,013,448	1,048,918	1,085,631
	AE costs (£)	63	412	561	581	601
	Non-progressive disease costs (routine care) (£)	53,589	351,277	478,384	495,127	512,457
	BSC costs(£)	36,838	241,472	328,847	340,357	352,270
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total current expenditure		**32,472,756**	**33,609,303**	**34,785,628**	**36,003,125**	**37,263,235**
Total future expenditure		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*All drug costs are based on anticipated list price for T-VEC and NHS list price for ipilimumab; BSC Best supportive care

6.9 Opportunities for resource savings or redirection of resources that it has not been possible to quantify

No other resource savings or redirection of resources is anticipated.

6.10 Main limitations within the budget impact analysis

Estimations of the total number of eligible patients treated with T-VEC were based on the estimated number of patients in Stage IIIB/C and IVM1a. Market share assumptions for the relevant comparators are based on limited evidence in the literature.

7 References

1. National Institute for Health and Care Excellence. *Dabrafenib for treating unresectable or metastatic BRAF V600 mutation ‑positive melanoma (TA321).* 2014.

2. National Institute for Health and Care Excellence. *Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA 319).* 2014.

3. Liu BL, Robinson M, Han ZQ, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene therapy.* Feb 2003;10(4):292-303.

4. Amgen. *Talimogene laherparepvec - EU summary of product characteristics.* 2015.

5. Andtbacka RHI, Collichio FA, Amatruda T, et al. Final planned overall survival (OS) from OPTiM, a randomized Phase III trial of talimogene laherparepvec (T-VEC) versus GM-CSF for the treatment of unresected stage IIIB/C/IV melanoma (NCT00769704). *Journal for immunotherapy of cancer.* 11/06 2014;2(Suppl 3):P263-P263.

6. Luke JJ, Hodi FS. Ipilimumab, vemurafenib, dabrafenib, and trametinib: synergistic competitors in the clinical management of BRAF mutant malignant melanoma. *The oncologist.* Jun 2013;18(6):717-725.

7. Medac. *Dacarbazine EU SmPC* 2014.

8. Merck. *Keytruda - EU SmPC.* 2015.

9. EMA. *Summary of opinion (initial authorisation): Imlygic (talimogene laherparepvec) EMA/690530/2015: Committee for Medicinal Products for Human Use (CHMP),.* 2015.

10. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. *The oncologist.* 2011;16(1):5-24.

11. Cancer Research UK. *Types of melanoma.* 2014.

12. Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. *Nature reviews. Cancer.* Apr 2009;9(4):274-284.

13. Cancer Research UK. *Types of skin cancer.* 2014.

14. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *American journal of surgery.* Jun 1978;135(6):807-810.

15. de la Monte SM, Moore GW, Hutchins GM. Patterned distribution of metastases from malignant melanoma in humans. *Cancer research.* Jul 1983;43(7):3427-3433.

16. Inagaki J, Rodriguez V, Bodey GP. Proceedings: Causes of death in cancer patients. *Cancer.* Feb 1974;33(2):568-573.

17. Kemp C. Lung cancer, malignant melanoma, multiple myeloma. *The American journal of hospice & palliative care.* May-Jun 1999;16(3):545-553.

18. Richard MA, Grob JJ, Avril MF, et al. Delays in diagnosis and melanoma prognosis (I): the role of patients. *International journal of cancer. Journal international du cancer.* May 20 2000;89(3):271-279.

19. Kamarashev JA SL, Zipser MC, Lockwood LL, Dummer R, Krengel S. *Melanocytic Tumors. In: R. Dummer et al. (eds) Skin Cancer - A Worldwide Perspective.* Springer Berlin Heidelberg; 2011.

20. Liu W, Dowling JP, Murray WK, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Archives of dermatology.* Dec 2006;142(12):1551-1558.

21. Brehmer F, Ulrich M, Haenssle HA. Strategies for early recognition of cutaneous melanoma-present and future. *Dermatology practical & conceptual.* Jul 2012;2(3):203a206.

22. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 20 2009;27(36):6199-6206.

23. Cancer Research UK. *Skin cancer incidence statistics.* 2014.

24. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British journal of cancer.* Dec 6 2011;105 Suppl 2:S77-81.

25. Cancer Research UK. *Skin cancer statistics.* 2014.

26. Cancer Research UK. *Skin cancer survival statistics.* 2014.

27. Garbe C, Leiter U. Melanoma epidemiology and trends. *Clinics in Dermatology.* 1// 2009;27(1):3-9.

28. Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics, 1994. *CA Cancer J Clin.* Jan-Feb 1994;44(1):7-26.

29. American Cancer Society. *Cancer Facts and Figures.* 2012.

30. Thiam A, Zhao Z, Weaver R, Quinn C, Barber B. Estimating Years of Life Lost Due to Advanced Melanoma in 12 Countries. *Value in Health.*17(3):A72.

31. Ekwueme DU, Guy GP, Jr., Li C, Rim SH, Parelkar P, Chen SC. The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006. *Journal of the American Academy of Dermatology.* Nov 2011;65(5 Suppl 1):S133-143.

32. Lebbe C, Lorigan P, Ascierto P, et al. Treatment patterns and outcomes among patients diagnosed with unresectable stage III or IV melanoma in Europe: a retrospective, longitudinal survey (MELODY study). *European journal of cancer.* Nov 2012;48(17):3205-3214.

33. Cashin RP, Lui P, Machado M, Hemels ME, Corey-Lisle PK, Einarson TR. Advanced cutaneous malignant melanoma: a systematic review of economic and quality-of-life studies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Mar-Apr 2008;11(2):259-271.

34. MacKie RM, Hauschild A, Eggermont AMM. Epidemiology of invasive cutaneous melanoma. *Annals of Oncology.* August 1, 2009 2009;20(suppl 6):vi1-vi7.

35. Elder DE, Guerry Dt, Heiberger RM, et al. Optimal resection margin for cutaneous malignant melanoma. *Plastic and reconstructive surgery.* Jan 1983;71(1):66-72.

36. Cassileth BR, Lusk EJ, Tenaglia AN. Patients' perceptions of the cosmetic impact of melanoma resection. *Plastic and reconstructive surgery.* Jan 1983;71(1):73-75.

37. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *The Lancet.*365(9460):687-701.

38. Lichtenthal WG, Cruess DG, Clark VL, Ming ME. Investment in body image among patients diagnosed with or at risk for malignant melanoma. *Body image.* Mar 2005;2(1):41-51.

39. Kasparian NA, McLoone JK, Butow PN. Psychological responses and coping strategies among patients with malignant melanoma: a systematic review of the literature. *Archives of dermatology.* Dec 2009;145(12):1415-1427.

40. Bonanno A, Esmaeli B, Fingeret MC, Nelson DV, Weber RS. Social challenges of cancer patients with orbitofacial disfigurement. *Ophthalmic plastic and reconstructive surgery.* Jan-Feb 2010;26(1):18-22.

41. Rigel DS, Robinson JK, Ross MI, al e. *Cancer of the Skin (2nd edition).* 2nd ed2011.

42. Bristow BN, Casil J, Sorvillo F, Basurto-Davila R, Kuo T. Melanoma-related mortality and productivity losses in the USA, 1990-2008. *Melanoma research.* Aug 2013;23(4):331-335.

43. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. *International journal of cancer. Journal international du cancer.* Feb 15 2015;136(4):E136-145.

44. Australian Cancer Network Melanoma Guidelines Revision Working Party. *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand.* 2008.

45. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica.* Oct 2007;92(10):1399-1406.

46. Bedikian AY, Johnson MM, Warneke CL, et al. Does complete response to systemic therapy in patients with stage IV melanoma translate into long-term survival? *Melanoma research.* Feb 2011;21(1):84-90.

47. BMS. Yervoy (ipilimumab) EU summary of product characteristics. 2015.

48. Genentech. Zelboraf (vemurafenib) EU summary of product characteristics. 2015.

49. Novartis. Tafinlar (dabrafenib) EU summary of product characteristics. 2015.

50. EMA. Committee for Medicinal Products for Human Use: Summary of opinion for Trametinib as monotherapy or in combination with dabrafenib. *23 July 2015: EMA/CHMP/444362/2015* 2015.

51. Novartis. Mekinist (trametinib) EU summary of product characteristics. 2015.

52. BMS. Opdivo (nivolumab) EU summary of product characteristics. 2015.

53. Merck. Keytruda (pembrolizumab) EU summary of product characteristics. 2015.

54. EMA. Committee for Medicinal Products for Human Use: Summary of opinion for cobimetinib in combination with vemurafenib. *24 September 2015: EMA/CHMP/571584/2015.* 2015.

55. National Institute for Health and Care Excellence. *Improving Outcomes for People with Skin Tumours including Melanoma (CGSTIM).* 2010.

56. National Institute for Health and Care Excellence. *Melanoma: assessment and management of melanoma (NG14).* 2015.

57. National Institute for Health and Care Excellence. *Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268).* 2012.

58. National Institute for Health and Care Excellence. *Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma (TA269).* 2012.

59. National Institute for Health and Care Excellence. *Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab - TA357.* 2015.

60. National Institute for Health and Care Excellence. *Pembrolizumab for advanced melanoma not previously treated with ipilimumab - Final appraisal determination [ID801].* 2015.

61. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised UK guidelines for the management of cutaneous melanoma 2010. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* Sep 2010;63(9):1401-1419.

62. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. *European journal of cancer.* Jan 2010;46(2):270-283.

63. Royal College of Physicians and British Association of Dermatologists. *The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. Concise guidance to good practice series, No 7.* London: RCP;2007.

64. Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G, Group EGW. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* Oct 2012;23 Suppl 7:vii86-91.

65. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. *J Clin Oncol.* Jun 20 2010;28(18):3042-3047.

66. Salama AK, de Rosa N, Scheri RP, et al. Hazard-rate analysis and patterns of recurrence in early stage melanoma: moving towards a rationally designed surveillance strategy. *PLoS One.* 2013;8(3):e57665.

67. MacMillan Cancer Support. We are MacMillan Cancer Support. Available at www.macmillan.org.uk. 2015: Accessed 21 July 2015.

68. Farr AM, Zhao Z, Song X, Barber BL, Ivanov B. Medical Costs by Disease Stage in Medicare Patients with Melanoma. *Value Health.* 2014;17(3):A78.

69. Alexandrescu DT. Melanoma costs: a dynamic model comparing estimated overall costs of various clinical stages. *Dermatol Online J.* 2009;15(11):1.

70. Hodi FS, Lee S, McDermott DF, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. *Jama.* Nov 5 2014;312(17):1744-1753.

71. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* Jun 30 2011;364(26):2507-2516.

72. Hodi FS, O'Day SJ, McDermott DF, Weber RW, al e. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine.* 2010;363(8):711-723.

73. Azarjana K, Ozola A, Ruklisa D, et al. Melanoma epidemiology, prognosis and trends in Latvia. *Journal of the European Academy of Dermatology and Venereology : JEADV.* Nov 2013;27(11):1352-1359.

74. Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. *Scientifica.* 2013;2013:857519.

75. EMA. *CHMP Assessment report: Zelboraf - vemurafenib (Procedure No.: EMEA/H/C/002409).* 2012.

76. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* Feb 23 2012;366(8):707-714.

77. Colombino M, Capone M, Lissia A, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 10 2012;30(20):2522-2529.

78. Sullivan RJ, Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. *European journal of cancer.* Apr 2013;49(6):1297-1304.

79. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Sep 1 2015;33(25):2780-2788.

80. Amgen. Data on file. 2015.

81. Nemunaitis JJ, Andtbacka RH, Ross M, et al. Results of the extension trial of OPTiM, a Multicenter, randomized phase 3 trial of talimogene laherparepvec (T-VEC) vs GM-CSF for Unresected stage IIIb-IV melanoma (Poster 1120P). *Annals of Oncology* 2014;25 (Supplement 4):iv374–iv393.

82. Harrington KJ, Andtbacka R, Collichio F, et al. Disease characteristics, treatment outcomes and safety with talimogene laherparepvec (T-VEC) vs GMCSF in patients with Stage IIIB-IVM1a melanoma in OPTiM. Paper presented at: 11th EADO Congress & 8th World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers (28-31 October)2015; Marseille, France.

83. University of York Centre for Reviews and Dissemination. *Systematic Reviews CRD's guidance for undertaking reviews in health care.* 2009.

84. Kaufman HLea. Primary overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. *J Clin Oncol.* 2014;32((suppl; abstr 9008a).).

85. Andtbacka RH KH, Collichio F, et al.,. Lower Risk of Visceral Metastasis in Patients With Stage IIIB/C/IVM1a Melanoma Treated With Talimogene Laherparepvec (T-VEC) vs GM-CSF in OPTiM (NCT00769704). Paper presented at: 68th SSO Annual Cancer Symposium2015; Houston, TX.

86. Andtbacka RHI RM, & Delman K,. Responses of Injected and Uninjected Lesions to Intralesional Talimogene Laherparepvec (T-VEC) in the OPTiM Study and the Contribution of Surgery to Response. Paper presented at: 67th SSO Annual Cancer Symposium2014; Phoenix, AZ

87. Yost KJ, Sorensen MV, Hahn EA, Glendenning GA, Gnanasakthy A, Cella D. Using multiple anchor- and distribution-based estimates to evaluate clinically meaningful change on the Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) instrument. *Value Health.* Mar-Apr 2005;8(2):117-127.

88. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* Jun 30 2011;364(26):2517-2526.

89. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 1 2015;33(10):1191-1196.

90. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *The Lancet. Oncology.* Mar 2014;15(3):323-332.

91. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* Jul 2 2015;373(1):23-34.

92. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety

analysis from a phase 3 trial in patients with advanced melanoma. *Cancer.* May 1 2013;119(9):1675-1682.

93. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* Oct 2013;24(10):2694-2698.

94. Harvey B, Lee D, Gaudin A-F, al. e. Changes in the quality of life of advanced melanoma patients after 12 weeks of treatment with ipilimumab compared to gp100 in a phase III clinical trial (abstr 9084). 2013 ASCO Annual Meeting; 2013.

95. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med.* Jun 25 2015;372(26):2521-2532.

96. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* Jan 1 2015;372(1):30-39.

97. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* Nov 13 2014;371(20):1877-1888.

98. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* Jul 2012;380(9839):358-365.

99. Hauschild A, Grob JJ, Demidov LV, al e. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM) (abstract 9013). Paper presented at: ASCO Annual Meeting; May 31-June 4, 2013; Chicago, IL.

100. Hauschild A, Grobb J, Demidov L, et al. [1092PD] An update on overall survival (OS) and follow-on therapies in BREAK-3, a phase III, randomized trial: dabrafenib (D) vs. Dacarbazine (DTIC) in patients (pts) with BRAF v600e mutation-positive metastatic melanoma (MM). *Annals of Oncology.* September 1, 2014 2014;25(suppl 4):iv378.

101. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* Nov 13 2014;371(20):1867-1876.

102. Andtbacka RH, Collichio F, Amatruda T, et al. Final planned overall survival (OS) from OPTiM, a randomized Phase III trial of talimogene laherparepvec (T-VEC) versus GM-CSF for the treatment of unresected stage IIIB/C/IV melanoma (NCT00769704). Paper presented at: 29th Annual Scientific Meeting of the Society for Immunotherapy of Cancer (SITC); 6-9 November, 2014; National Harbor, MD, USA.

103. Korn EL, Liu PY, Lee SJ, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 1 2008;26(4):527-534.

104. Agarwala SS, Keilholz U, Gilles E, et al. LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). *European journal of cancer.* Jul 2009;45(10):1807-1814.

105. Tas F, Oguz H, Argon A, et al. The value of serum levels of IL-6, TNF-alpha, and erythropoietin in metastatic malignant melanoma: serum IL-6 level is a valuable prognostic factor at least as serum LDH in advanced melanoma. *Medical oncology.* 2005;22(3):241-246.

106. Smit LH, Korse CM, Hart AA, et al. Normal values of serum S-100B predict prolonged survival for stage IV melanoma patients. *European journal of cancer.* Feb 2005;41(3):386-392.

107. Keilholz U, Martus P, Punt CJ, et al. Prognostic factors for survival and factors associated with long-term remission in patients with advanced melanoma receiving cytokine-based treatments: second analysis of a randomised EORTC Melanoma Group trial comparing interferon-alpha2a (IFNalpha) and interleukin 2 (IL-2) with or without cisplatin. *European journal of cancer.* Jul 2002;38(11):1501-1511.

108. Banfalvi T, Boldizsar M, Gergye M, Gilde K, Kremmer T, Otto S. Comparison of prognostic significance of serum 5-S-Cysteinyldopa, LDH and S-100B protein in Stage III-IV malignant melanoma. *Pathology oncology research : POR.* 2002;8(3):183-187.

109. Manola J, Atkins M, Ibrahim J, Kirkwood J. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Nov 15 2000;18(22):3782-3793.

110. Proebstle TM, Fuchs T, Scheibenbogen C, Sterry W, Keilholz U. Long-term outcome of treatment with dacarbazine, cisplatin, interferon-alpha and intravenous high dose interleukin-2 in poor risk melanoma patients. *Melanoma research.* Dec 1998;8(6):557-563.

111. Franzke A, Probst-Kepper M, Buer J, et al. Elevated pretreatment serum levels of soluble vascular cell adhesion molecule 1 and lactate dehydrogenase as predictors of survival in cutaneous metastatic malignant melanoma. *British journal of cancer.* Jul 1998;78(1):40-45.

112. Eton O, Legha SS, Moon TE, et al. Prognostic factors for survival of patients treated systemically for disseminated melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Mar 1998;16(3):1103-1111.

113. Sirott MN, Bajorin DF, Wong GY, et al. Prognostic factors in patients with metastatic malignant melanoma. A multivariate analysis. *Cancer.* Nov 15 1993;72(10):3091-3098.

114. Kotapati S, Dequen P, Ouwens M. Overall survival (OS) in the management of pretreated patients with unresectable stage III/IV melanoma: A systematic literature review and meta-analysis. *Journal of Clinical Oncology.* 2011;29.

115. Senzer NN, Kaufman HL, Amatruda T, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 1 2009;27(34):5763-5771.

116. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2012, (available at: http://seer.cancer.gov/csr/1975_2012/).* National Cancer Institute. Bethesda, MD2014.

117. Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. (Available from: http://globocan.iarc.fr).* Lyon, France: International Agency for Research on Cancer2012.

118. Scottish Medicines Consortium. *ipilimumab (Yervoy): SMC No. (997/14).* 2012.

119. Scottish Medicines Consortium. *vemurafenib 240mg film-coated tablet (Zelboraf®) SMC No. (792/12).* 2013.

120. Scottish Medicines Consortium. *dabrafenib, 50mg and 75mg hard capsules (Tafinlar®) SMC No. (No.1023/15).* 2015.

121. Lee NR, Lee SH, Kim J, Son SK, Seo HJ, Park DA. Cost-utility analysis of dabrafenib/trametinib combination (D+T) for BRAFv600 mutation-positive metastatic melanoma (mm) from the United Kingdom (UK) National Health Service (NHS) perspective. *Value in Health.* 2014;17(3):A71.

122. Lee D, Winn B, Lebmeier M. Modelling the cost-effectiveness of ipilimumab for previously-treated, metastatic melanoma. . *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2012;15: A423.

123. Scottish Medicines Consortium. *ipilimumab (Yervoy): SMC No. (779/12).* 2012.

124. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ (Clinical research ed.).* Aug 3 1996;313(7052):275-283.

125. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal. National Institute for Health and Care Excellence. (Available at: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf. Accessed May 14, 2015).* 2013.

126. Office for National Statistics. *National Life Tables, United Kingdom, 2011-2013 (Available at: http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2011-2013/stb-uk-2011-2013.html).* 2014.

127. Latimer N. *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available at: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.pdf.* 2011

128. Gould W. Chow tests. http://www.stata.com/support/faqs/statistics/chow-tests/. 2011.

129. Chow GC. Tests of Equality Between Sets of Coefficients in Two Linear Regressions. Available at: http://www.jstor.org/discover/10.2307/1910133?uid=3738032&uid=2&uid=4&sid=21104621091073. *Econometrica* 1960;28:591-605.

130. Beusterien KM, Szabo SM, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *British journal of cancer.* Aug 4 2009;101(3):387-389.

131. Batty A, Winn B, Lebmeier M, Rowen D, Lee D. CA4 A Comparison of Patient and General-Population Utility Values for Advanced Melanoma in Health Economic Modelling. *Value in Health.* 2012;15(7):A285.

132. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. *Health Qual Life Outcomes.* 2014;12:140.

133. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* Jan 22 2015;372(4):320-330.

134. ClinicalTrials.gov. Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination With Ipilimumab vs Ipilimumab Alone in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma (CheckMate 069). 2015.

135. Mols F, Holterhues C, Nijsten T, van de Poll-Franse LV. Personality is associated with health status and impact of cancer among melanoma survivors. *European journal of cancer.* Feb 2010;46(3):573-580.

136. Amgen. Data on file: A bespoke utility study for advanced melanoma. 2014.

137. Johnston K, Levy AR, Lorigan P, et al. Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study). *European journal of cancer.* Sep 2012;48(14):2175-2182.

138. Lorigan P, Marples M, Harries M, et al. Treatment patterns, outcomes, and resource utilization of patients with metastatic melanoma in the U.K.: the MELODY study. *The British journal of dermatology.* Jan 2014;170(1):87-95.

139. Liniker E, Harrison M, Weaver JMJ, et al. Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009-2010). *British journal of cancer.* 10/15/print 2013;109(8):2051-2057.

140. Amgen. Data on file: costing the treatment pathway in advanced melanoma. 2014.

141. Department of Health. *NHS Reference Costs (2013-2014).* 2014.

142. Addicott R, Dewar S. *Improving choice at end of life. A descriptive analysis of the impact and costs of the Marie Curie delivering choice programme in Lincolnshire* 2008.

143. British National Formulary. BNF online. Available at: http://www.bnf.org/products/bnf-online/. 2015.

144. Personal Social Services Research Unit. *Unit costs of health and social care. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2012/. Accessed May 14, 2015.* 2012.

145. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *Journal of clinical oncology*

: official journal of the American Society of Clinical Oncology. Apr 1 2011;29(10):1239-1246.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talimogene laherparepvec for treating metastatic melanoma

Patient access scheme submission template

January 2016

File name	Version	Contains confidential information	Date
		Yes CIC: Highlighted in turquoise and underlined	January 2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: Talimogene laherparepvec (brand name: Imlygic)

Disease area: Unresectable metastatic melanoma; talimogene laherparepvec is indicated "for the treatment of adults with unresectable melanoma that regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease"

3.2 Please outline the rationale for developing the patient access scheme.

The rationale behind the patient access scheme is to provide talimogene laherparepvec at a cost-effective price to the NHS, mitigating any risk to the NHS due to limitations of the evidence base of ipilimumab and other comparator treatments in the licensed population for talimogene laherparepvec.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The proposed patient access scheme is a simple scheme (confidential discount off the NHS list price of the10^6pfu/mL x1mL and 10^8pfu/mL x1mL vials of talimogene laherparepvec). The proposed confidential discount is [redacted]. The scheme is expected to be implemented at the time of positive NICE guidance, expected in July 2016.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme applies to the whole population for which talimogene laherparepvec is licensed, i.e. for adults with unresectable melanoma that regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any additional criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Not applicable.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The price (including the patient access scheme confidential discount) will be demonstrated to NHS organisations on the original invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See above.

3.10 Please provide details of the duration of the scheme.

The patient access scheme will remain in place until NICE next reviews the product under the technology appraisals programme and a final decision has been published by NICE (as per the declaration signed by Amgen in the patient access scheme proposal template).

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The patient access scheme does not require any additional forms, registration or other administrative process to claim the discount.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The patient access scheme applies to the entire licensed population for talimogene laherparepvec – the population presented in the main submission of evidence.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Patient access scheme is likely to be approved prior to the first Appraisal Committee meeting. No changes have been made to the model.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The patient access scheme has been incorporated into the economic model by utilising the discounted price per vial for talimogene laherparepvec that would apply in the context of a simple discount. The NHS list price of talimogene laherparepvec is £1,670 per vial (10^6pfu/mL x1mL and 10^8pfu/mL

x1mL vials). It is noteworthy that the anticipated NHS list price for talimogene laherparepvec in the manufacturer submission has been updated and no longer holds and the final NHS list price is £1,670 (confirmed with the Department of Health). The patient access scheme is a fixed price of [redacted] per vial (10^6pfu/mL x1mL and 10^8pfu/mL x1mL vials). The patient access scheme (talimogene laherparepvec drug cost) has been implemented in the economic model in the 'Drug Costs' worksheet and descriptively in the 'Drug Cost Calcs' worksheet.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data for talimogene laherparepvec from the pivotal OPTiM trial is presented in Table 1. This data underpins the economic model in the evidence submission and remains the same regardless of the implementation of the patient access scheme.

Table 1: Key outcomes from the OPTiM trial (Stage IIIB, IIIC and IVM1a with no bone, brain, lung or other visceral disease population)

Talimogene laherparepvec (OPTiM) Final descriptive data cut 8th August 2014		
Outcome	**T-VEC (N = 163)**	**GM-CSF (N = 86)**
Median OS months (95% CI)	46.8 (31.2, NE)	21.5 (17.4, 29.6)
HR (95% CI); p-value	0.56 (0.40, 0.79); p=0.0008	
Median PFS (months) (95% CI)	13.1 (8.3, NE)	3.3 (2.8, 4.3)
HR (95% CI); p-value	0.27 (0.19, 0.39); p=<0.0001	
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival (Time to treatment failure [TTF] used as proxy); NE, not estimable; T-VEC, talimogene laherparepvec.		

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There will be no costs associated with the implementation and operation of the proposed patient access scheme as this scheme involves a simple confidential discount of [redacted] applied at the point of order.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of the patient access scheme will not incur additional treatment-related costs.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Our manufacturer's evidence submission presents the cost-effectiveness results for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

anticipated NHS list price for talimogene laherparepvec no longer holds and the final NHS list price is £1,670. The results using the final NHS list price are presented in Table 2 below. The cost-effectiveness results including the proposed patient access scheme for talimogene laherparepvec are presented in Table 3.

Table 2 Base-case cost-effectiveness results (NHS list price [without PAS])

	Ipilimumab	Talimogene laherparepvec
Modified Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£28,752	£35,561
Adverse event costs	£118	£3
Total costs	£98,219	[redacted]
Difference in total costs	NA	[redacted]
LYG	4.90	6.66
LYG difference	NA	1.76
QALYs	3.57	4.91
QALY difference	NA	1.34
ICER (£ per QALY gained)	NA	[redacted]
Two-step Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£26,567	£34,419
Adverse event costs	£118	£3
Total costs	£96,035	[redacted]
Difference in total costs	NA	[redacted]
LYG	6.16	6.66
LYG difference	NA	0.50
QALYs	4.61	4.95
QALY difference	NA	0.35
ICER (£ per QALY gained)	NA	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable.

Table 3 Base-case cost-effectiveness results (with PAS)

	Ipilimumab	Talimogene laherparepvec
Modified Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£28,752	£35,561
Adverse event costs	£118	£3
Total costs	£98,219	[redacted]
Difference in total costs	NA	[redacted]
LYG	4.90	6.66
LYG difference	NA	1.76
QALYs	3.57	4.91
QALY difference	NA	1.34
ICER	NA	-£16,367
Two-step Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£26,567	£34,419
Adverse event costs	£118	£3
Total costs	£96,035	[redacted]
Difference in total costs	NA	[redacted]
LYG	6.16	6.66
LYG difference	NA	0.50
QALYs	4.61	4.95
QALY difference	NA	0.35
ICER (£ per QALY gained)	NA	-£60,271

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable; PAS, patient access scheme.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 4 Base-case incremental results (NHS list price [without PAS])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Modified Korn							
Ipilimumab	[redacted]	4.90	3.57	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.91	[redacted]	1.76	1.34	[redacted]
Two-Step Korn							
Ipilimumab	[redacted]	6.16	4.61	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.95	[redacted]	0.50	0.35	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable.

Table 5 Base-case incremental results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Modified Korn							
Ipilimumab	[redacted]	4.90	3.57	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.91	[redacted]	1.76	1.34	-£16,367
Two-Step Korn							
Ipilimumab	[redacted]	6.16	4.61	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.95	[redacted]	0.50	0.35	-£60,271

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable; PAS, patient access scheme.

Ipilimumab is available with an approved PAS (simple confidential discount) to the NHS. Given the confidential nature of the PAS, a comparison of the ICERs using a range of simple discounts (from 0%-100%) to reflect the possible PAS price for ipilimumab is presented in Table 6 below. It should be noted that these results are based on the PAS price for talimogene laherparepvec.

Table 6 Comparison of ICERs assuming a range of potential discounts for ipilimumab with PAS price for talimogene laherparepvec

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
0%	[redacted]	[redacted]
5%	[redacted]	[redacted]
10%	[redacted]	[redacted]
15%	[redacted]	[redacted]
20%	[redacted]	[redacted]
25%	[redacted]	[redacted]
30%	[redacted]	[redacted]
35%	[redacted]	[redacted]
40%	[redacted]	[redacted]
45%	[redacted]	[redacted]
50%	[redacted]	[redacted]
55%	[redacted]	[redacted]
60%	[redacted]	[redacted]
65%	[redacted]	[redacted]
70%	[redacted]	[redacted]
75%	[redacted]	[redacted]
80%	[redacted]	[redacted]
85%	[redacted]	[redacted]
90%	[redacted]	[redacted]
95%	[redacted]	[redacted]
100%	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year		

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Our manufacturer's evidence submission presents the results of the deterministic sensitivity analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The anticipated list price for talimogene laherparepvec is no longer valid and Figure 1 below presents results using the final NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results including the proposed patient access scheme for talimogene laherparepvec are presented in Figure 2.

Figure 1 Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, with NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

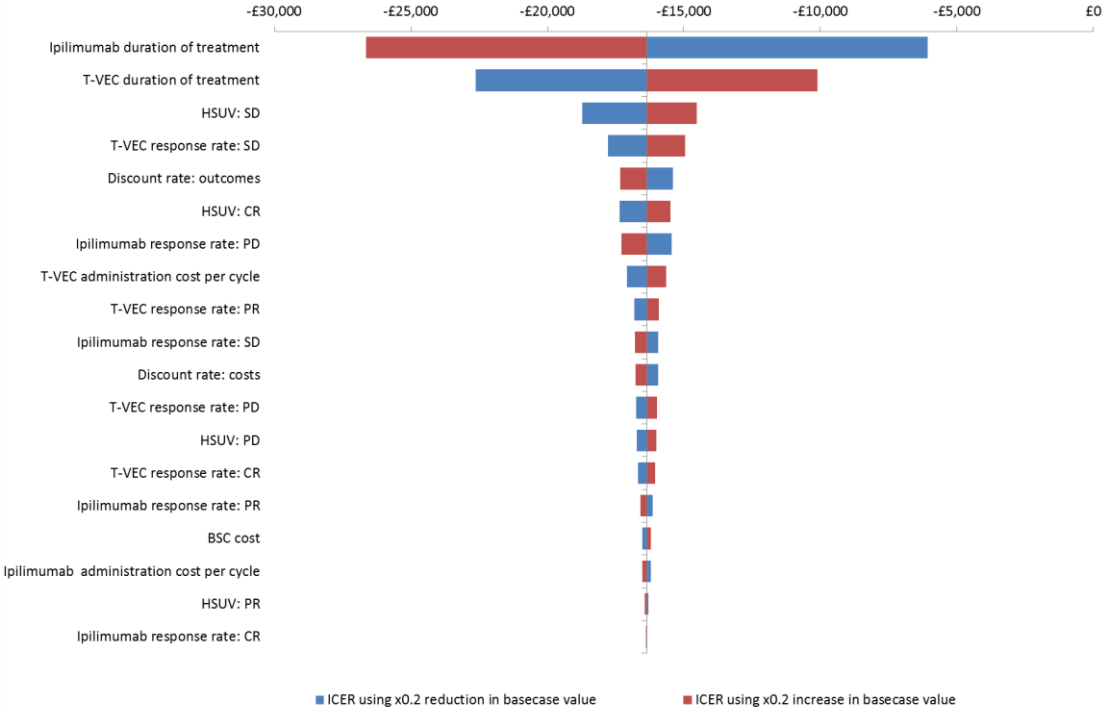
b. Using Two-Step Korn Adjustment

[redacted]

T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

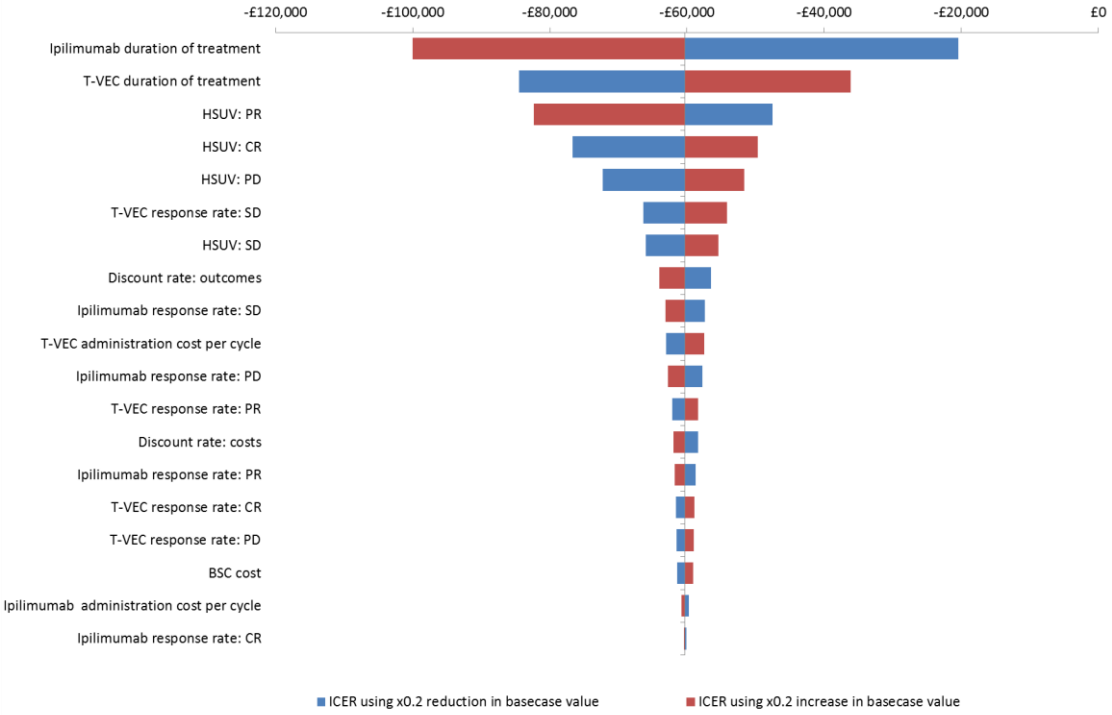
Figure 2 Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, including the patient access scheme for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR: partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

b. Using Two-Step Korn Adjustment



T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Our manufacturer's evidence submission presents the results of the probabilistic sensitivity analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results using the final NHS list price are presented in Table 7 below. The results including the proposed patient access scheme for talimogene laherparepvec are presented in Table 8.

Table 7 Incremental cost-effectiveness results based on PSA (NHS list price [without PAS])

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs (95% CI)
Modified Korn					
Ipilimumab	[redacted]	3.55 (3.08 to 3.94)	[redacted]	1.23 (0.58 to 1.68)	[redacted]
Talimogene laherparepvec	[redacted]	4.78 (3.97 to 5.41)			
Two-step Korn					
Ipilimumab	[redacted]	4.59 (4.20 to 4.93)	[redacted]	0.25 (-0.53 to 0.78)	[redacted]
Talimogene laherparepvec	[redacted]	4.84 (3.96 to 5.41)			

CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Table 8 Incremental cost-effectiveness results based on PSA (with PAS)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs (95% CI)
Modified Korn					
Ipilimumab	[redacted]	3.56 (3.12 to 3.92)	[redacted]	1.24 (0.54 to 1.73)	-£27,730 (Dominant) (-£43,936 to -£3,903)
Talimogene laherparepvec	[redacted]	4.80 (4.00 to 5.40			
Two-step Korn					
Ipilimumab	[redacted]	4.58 (4.18 to 4.95)	[redacted]	0.26 (-0.44 to 0.79)	-£1,668,400 (Dominant) (-£557,874 to £556,979)
Talimogene laherparepvec	[redacted]	4.85 (4.10 to 5.39)			

CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life-year

Figure 3 to Figure 8 present the results using scatter plots and cost-effectiveness acceptability curves.

Figure 3 Scatterplot of PSA results (1,000 simulations; results discounted, NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

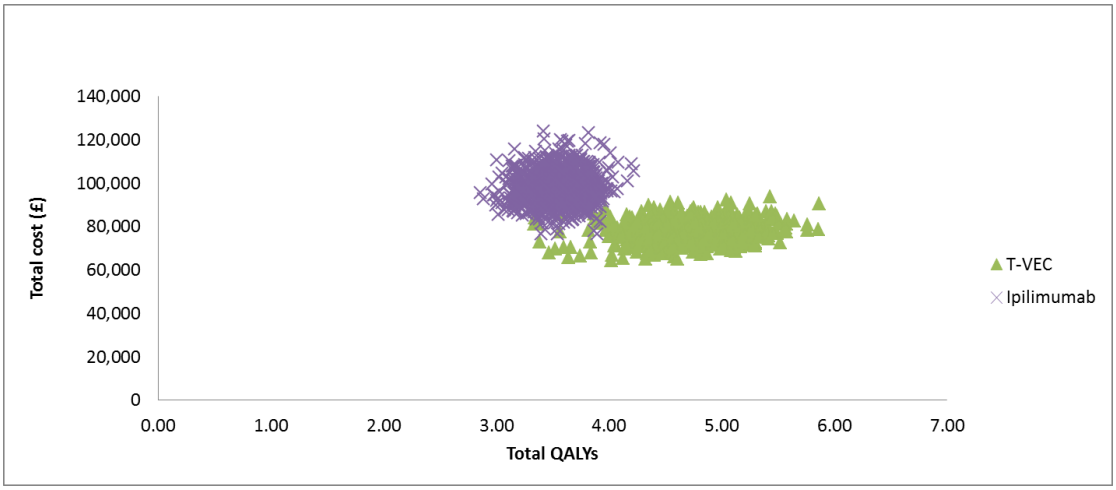
PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

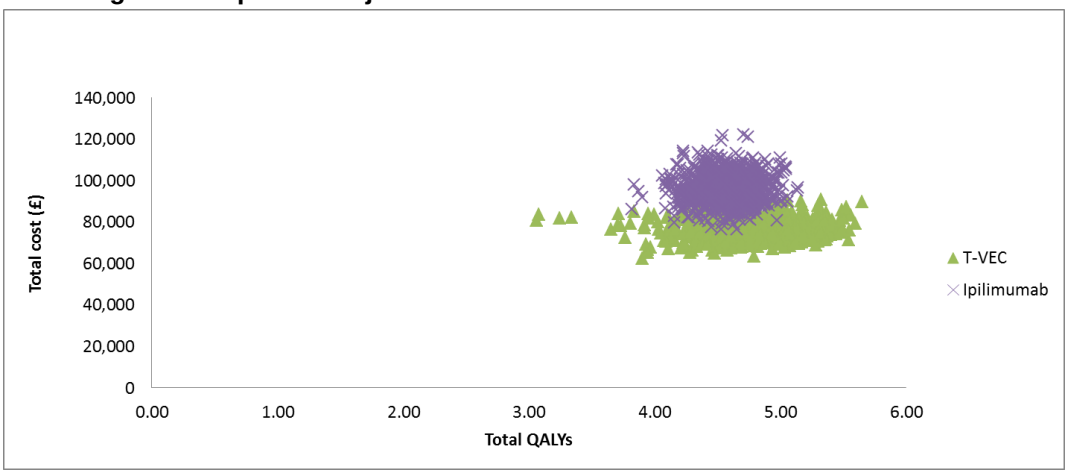
Figure 4 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

Figure 5 Scatterplot of PSA results (1,000 simulations; results discounted, NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

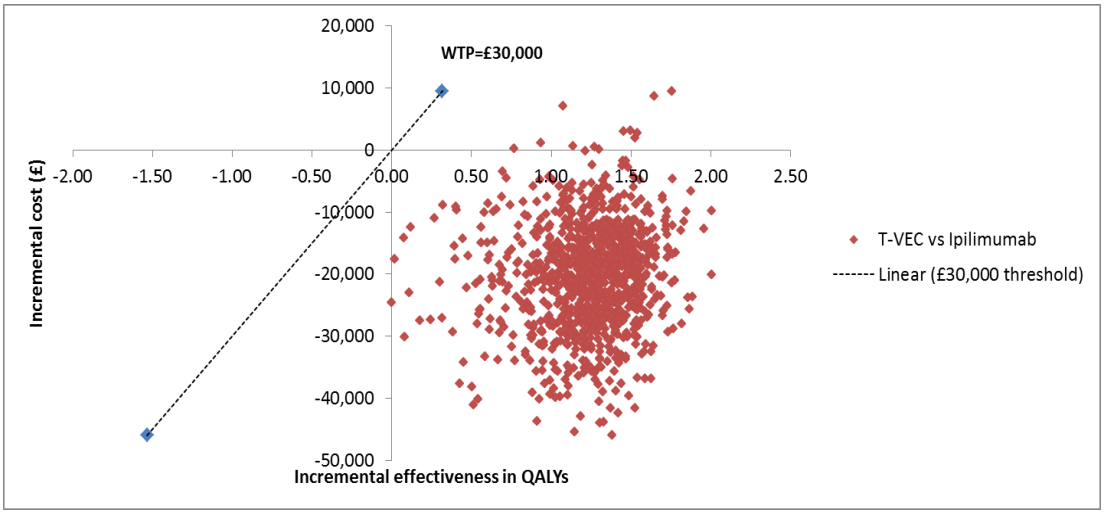
PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

b. Using Two-Step Korn Adjustment

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

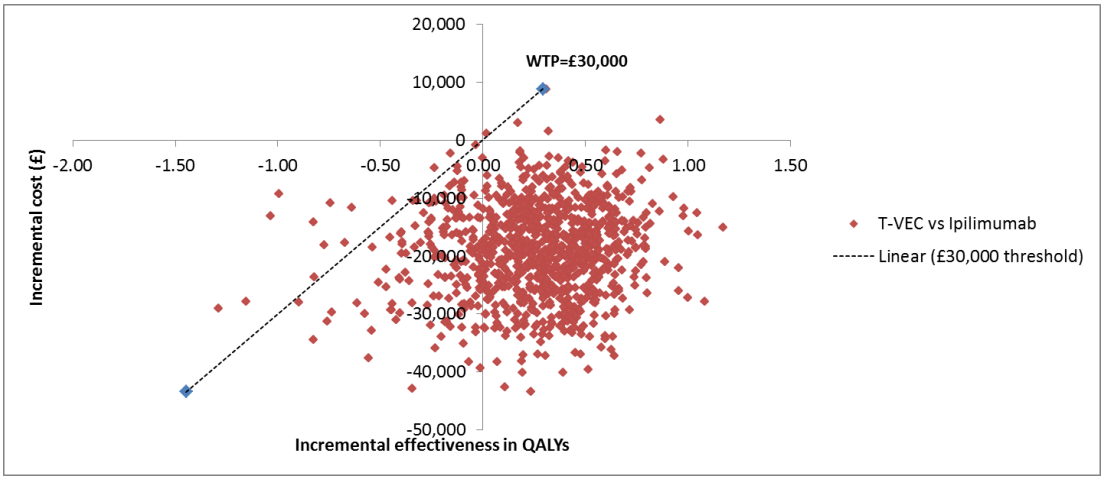
Figure 6 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

b. Using Two-Step Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

Figure 7 Cost-effectiveness acceptability curve (results discounted, with NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

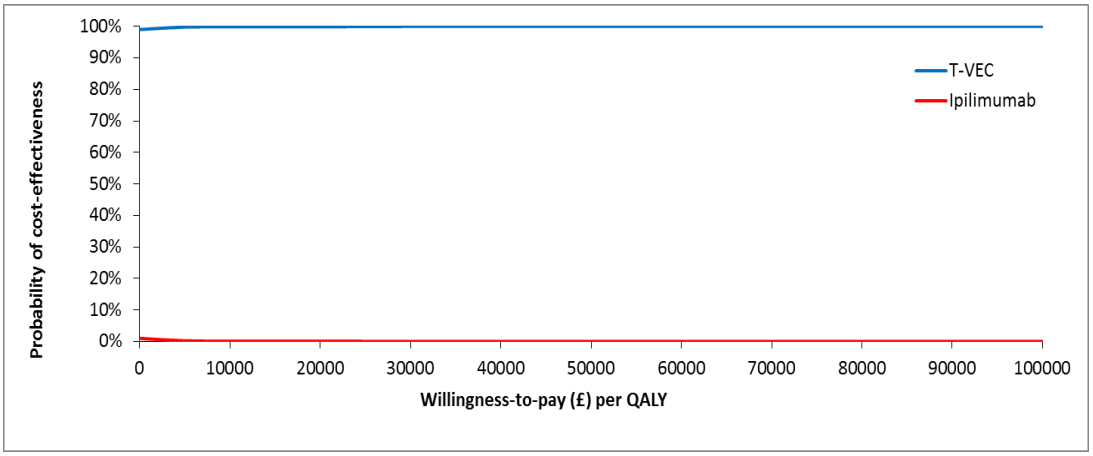
QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment

QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

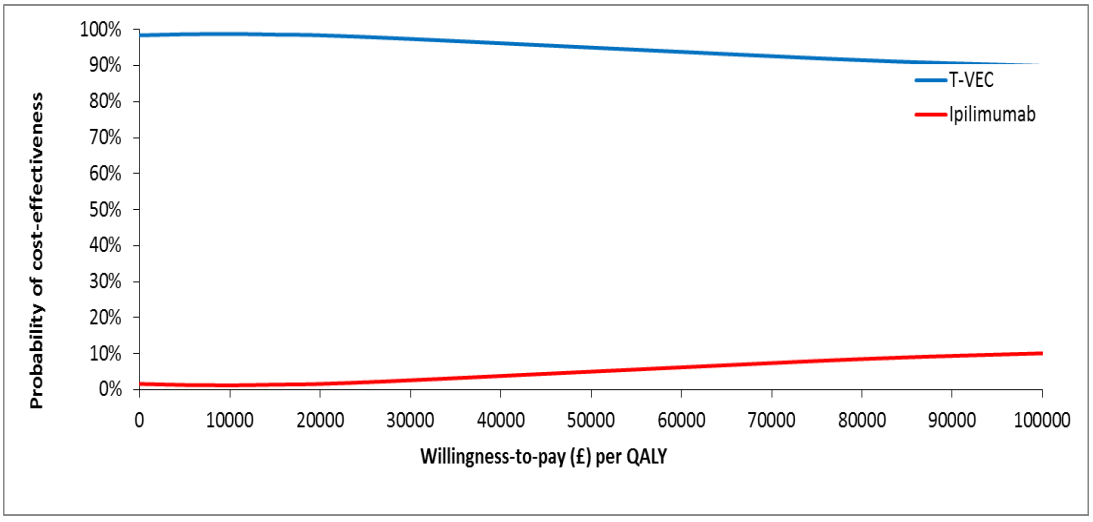
Figure 8 Cost-effectiveness acceptability curve (results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment



QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Our manufacturer's evidence submission presents the results of the scenario analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results using the final NHS list price are presented in Table 9 below.

Table 9 Results of the scenario analyses (NHS list price [without PAS])

Parameter	Base Case assumptions	Sensitivity Analysis	Modified Korn ICER	Two-Step Korn ICER
			£/QALY	£/QALY
Base case result:			[redacted]	[redacted]
Varying the time horizon				
Time horizon	30 years	10 years	[redacted]	[redacted]
		20 years	[redacted]	[redacted]
		25 years	[redacted]	[redacted]
Varying the modelling approach for T-VEC dosing				
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection[redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]

		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]
Varying the modelling approach for IPI dosing				
IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	[redacted]	[redacted]
Varying the approach to modelling utilities				
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al., 2009 (PR = 0.85, SD = 0.77, PD = 0.59; as no value was reported for CR, it is assumed to have the same value as PR)	[redacted]	[redacted]
		IPI 1 L (TA268) (SD = 0.81, PD = 0.77; as no values were reported for CR and PR, they are assumed to have the same value as SD)	[redacted]	[redacted]
		Amgen TTO study (CR = 0.84, PR = 0.73, SD = 0.69, PD = 0.45)	[redacted]	[redacted]
Alternative parametric curve fits				
OS	Exponential	Log-normal	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]
PFS	Generalised gamma	Log-normal	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]
Alternative approach to modelling survival				
OS	3-part curve fit	2-part curve fit	[redacted]	[redacted]
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	[redacted]

Varying resource use assumptions in terminal care				
Cost of terminal care	Amgen resource use study	TA319 (£6,211.006 [inflated from 2012 cost to 2015 cost])	[redacted]	[redacted]
Varying resource use assumptions in routine treatment for non-progressive disease				
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR were £0.00 for both T-VEC and IPI	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	[redacted]
BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; QALY, quality-adjusted life-year; SD, stable disease; SPC, summary of product characteristics; TTO, time trade off; T-VEC, talimogene laherparepvec				

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

The cost-effectiveness results of scenario analyses including the proposed patient access scheme for talimogene laherparepvec are presented in Table 10 below.

Table 10 Results showing the impact of patient access scheme on ICERs

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
Base case result:			[redacted]	-£16,367	[redacted]	-£60,271
Varying the time horizon						
Time horizon	30 years	10 years	[redacted]	-£28,575	[redacted]	-£116,708
		20 years	[redacted]	-£18,867	[redacted]	-£71,402
		25 years	[redacted]	-£17,193	[redacted]	-£63,624
Varying the modelling approach for T-VEC dosing						
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	-£14,704	[redacted]	-£53,840

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	-£19,389	[redacted]	-£71,957
Varying the modelling approach for IPI dosing						
IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	[redacted]	-£21,253	[redacted]	-£79,163

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
Varying the approach to modelling utilities						
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al., 2009 (PR = 0.85, SD = 0.77, PD = 0.59; as no value was reported for CR, it is assumed to have the same value as PR)	[redacted]	-£16,163	[redacted]	-£69,918
		IPI 1 L (TA268) (SD = 0.81, PD = 0.77; as no values were reported for CR and PR, they are assumed to have the same value as SD)	[redacted]	-£15,431	[redacted]	-£53,870
		Amgen TTO study (CR = 0.84, PR = 0.73, SD = 0.69, PD = 0.45)	[redacted]	-£17,701	[redacted]	-£71,742
Alternative parametric curve fits						
OS	Exponential	Log-normal	[redacted]	-£14,644	[redacted]	-£48,610
		Weibull	[redacted]	-£14,601	[redacted]	-£47,977
PFS	Generalised gamma	Log-normal	[redacted]	-£18,338	[redacted]	-£88,189

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
		Log-logistic	[redacted]	-£18,380	[redacted]	-£87,422
Alternative approach to modelling survival						
OS	3-part curve fit	2-part curve fit	[redacted]	-£14,108	[redacted]	-£27,241
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	-£16,739	[redacted]	-£59,667
Varying resource use assumptions in terminal care						
Cost of terminal care	Amgen resource use study	TA319 (£6,211.006 [inflated from 2012 cost to 2015 cost])	[redacted]	-£16,372	[redacted]	-£60,277
Varying resource use assumptions in routine treatment for non-progressive disease						
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR were £0.00 for both T-VEC and IPI	[redacted]	-£17,769	[redacted]	-£65,967
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	-£17,310	[redacted]	-£63,722
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	-£15,424	[redacted]	-£56,820

BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; OS, overall survival; PAS, patient access scheme; PD, progressive disease; PFS, progression-free survival; PR, partial response; QALY, quality-adjusted life-year; SD, stable disease; SPC, summary of product characteristics; TTO, time trade off; T-VEC, talimogene laherparepvec

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Dear [redacted]

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at the submission received on 6th November 2015 by Amgen. 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.

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

Please provide your written response to the clarification questions by **5pm** on **10th December 2015**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals **https://appraisals.nice.org.uk/request/9531**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information 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.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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 [redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

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

A1. **Priority question.** 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.

A2. **Priority question.** 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

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

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.

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.

A3. **Priority question.** 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.

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 **Error! Reference source not found.** above).

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

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

A7. **Priority question.** 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.

A8. **Priority question.** 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.

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.

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.

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.

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).

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.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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)

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.

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.

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

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

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.

A18. In relation to A17.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.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section B: Clarification on cost-effectiveness data

N.B. When referring to PFS data below, the ERG is referring to the data labelled PFS in the company's economic model.

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).

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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

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

B2. **Priority question: 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.

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 **Error! Reference source not found.**.

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.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

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.

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

Treatment cycle	Patients still on treatment	Total vials used in cycle
2	n_2	v_2
3	n_3	v_3
4	n_4	v_4
5	n_5	v_5
6	n_6	v_6
…	…	…

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.

Section 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.

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.

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.

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

List of tables

List of figures

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:

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

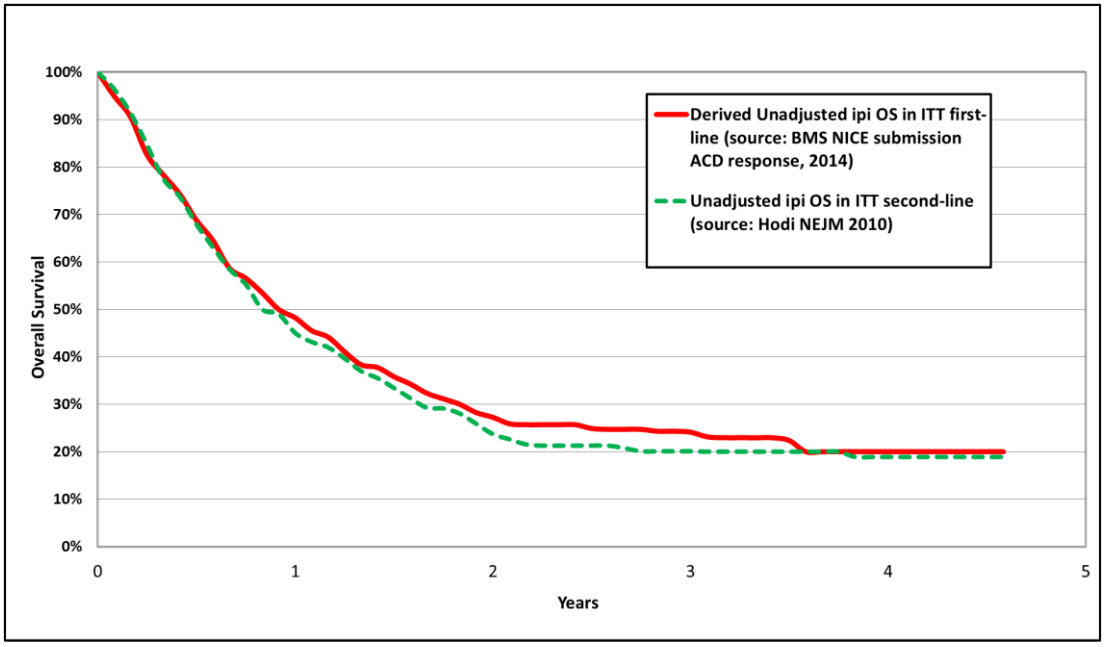
c. For Table 4-24, please provide further details on the methodology used to derive the overall survival (OS) estimate for the monotherapy ipilimumab 3mg/kg group, as used in the company's submission in the NICE technology appraisal of ipilimumab for previously untreated (unresectable or metastatic)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

A3 (Priority question). 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

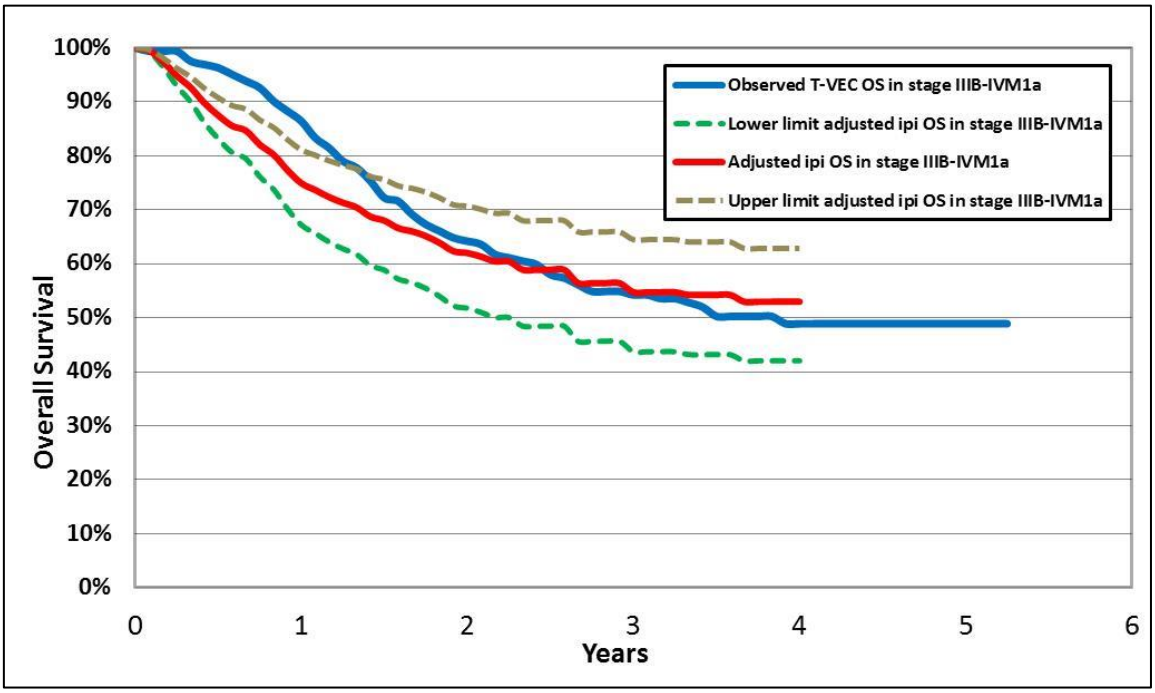
	Unadjusted PFS	Two-step Korn
Median		
T-VEC	13.1	–
Ipilimumab pooled	2.8	17.6
Mean (AUC)[a]		
T-VEC	18.2	–
Ipilimumab pooled	7.4	18.6

[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.

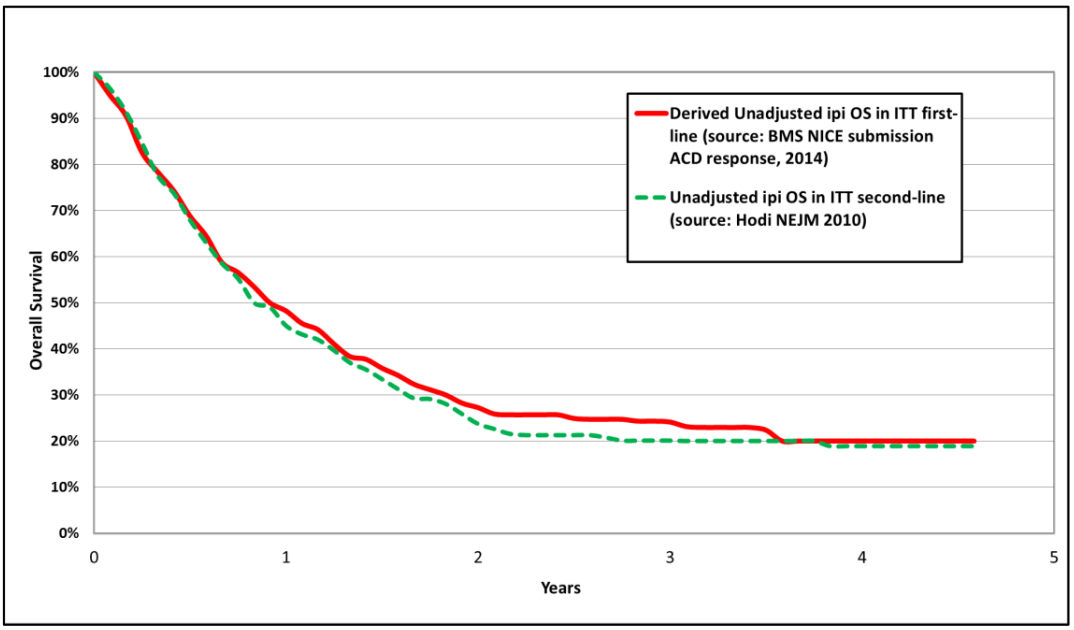
<u>A7 (Priority question).</u> Please justify why it is appropriate to pool data from both the ipilimumab monotherapy and ipilimumab + dacarbazine arms, and from trials of both previously treated and previously untreated patients. Please clarify whether the heterogeneity that may arise from these differences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

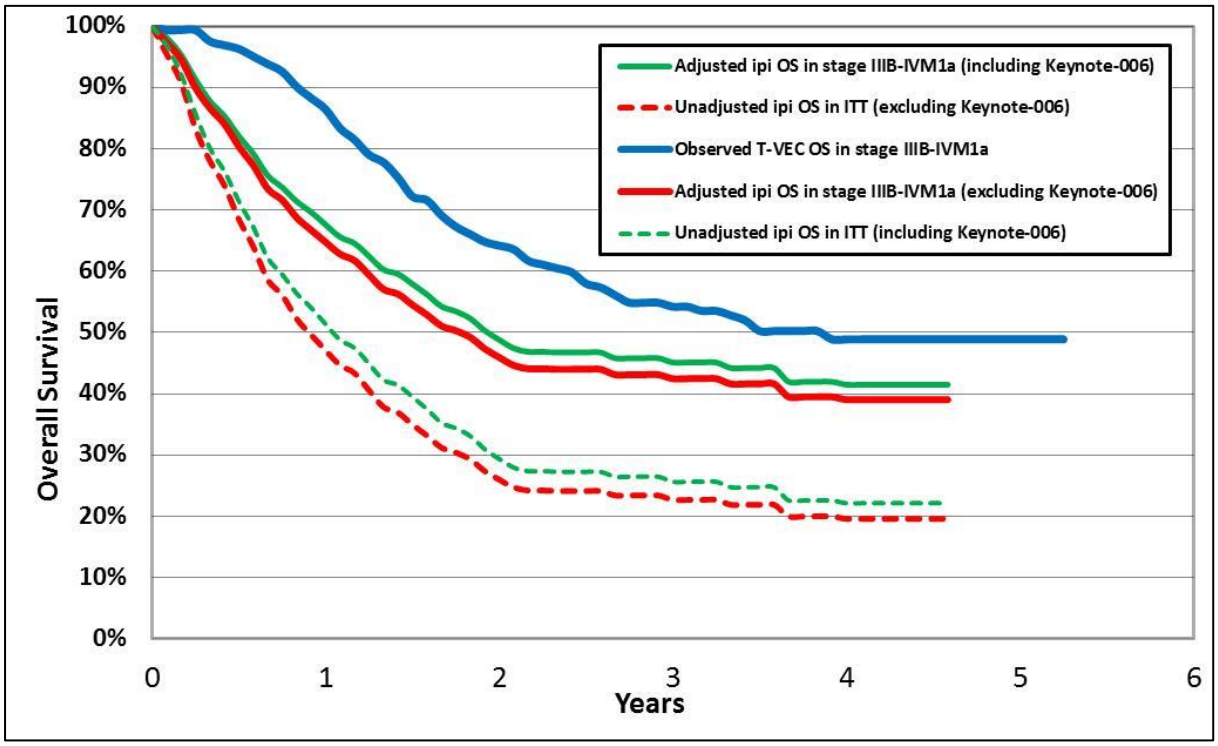
A8 (Priority question). Please clarify why the company did not include, in its analyses using the Korn algorithm, data from the CheckMate 067 and KEYNOTE 006 trials. If possible, please provide Korn adjusted OS and PFS estimates for ipilimumab (using both the modified and two-step methods) based on analyses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

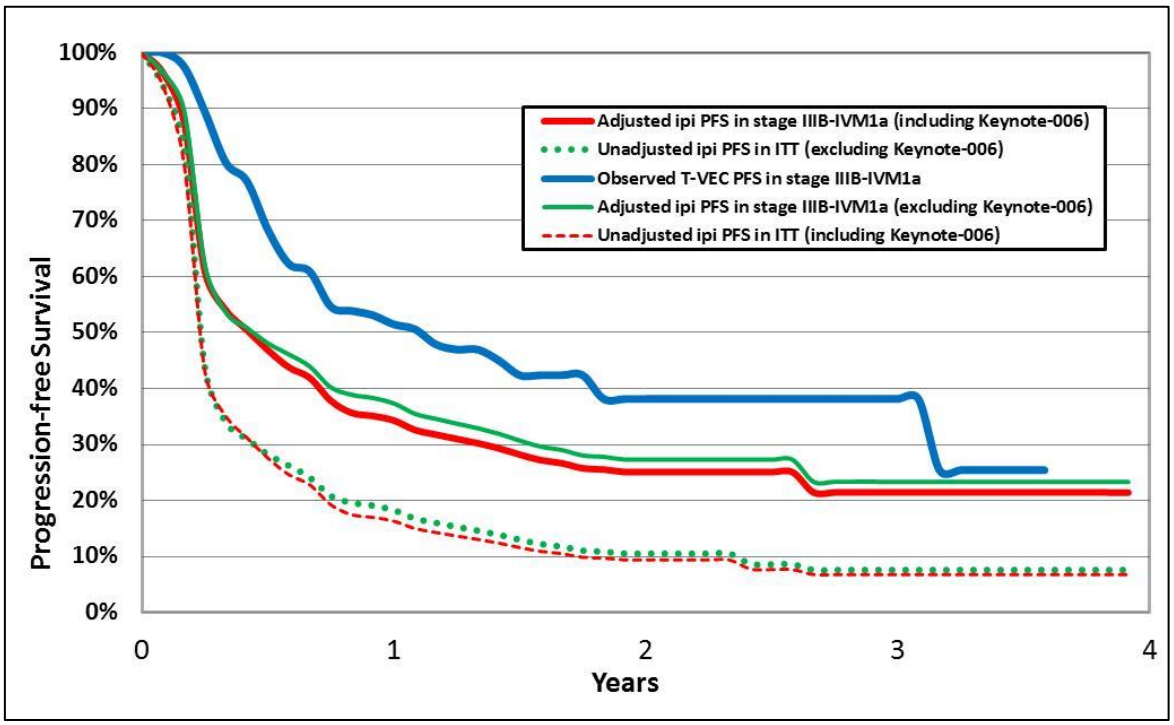
We provide below, the results from the modified Korn method when the KEYNOTE 006 trial data for ipilimumab is included (Figure A-4, Figure A-5, Table A-8 and Table A-9). The impact of including data from KEYNOTE 006 is small: the mean OS for ipilimumab is increased from 29.2 to 30.6 months, compared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

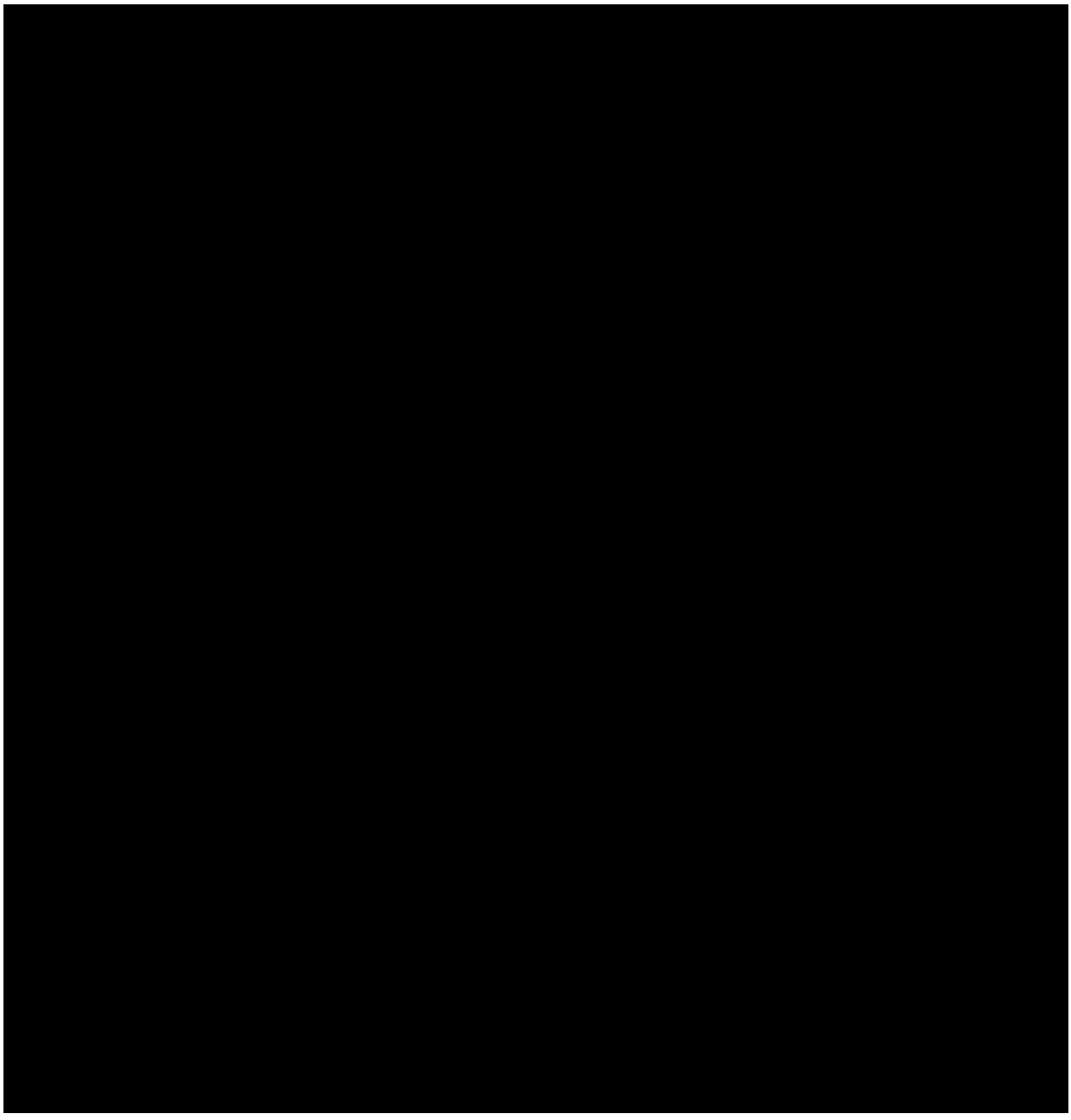
CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent-to-treat; NE, not estimable; PDr, clinically relevant disease progression; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

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)



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)

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.

A18. 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.

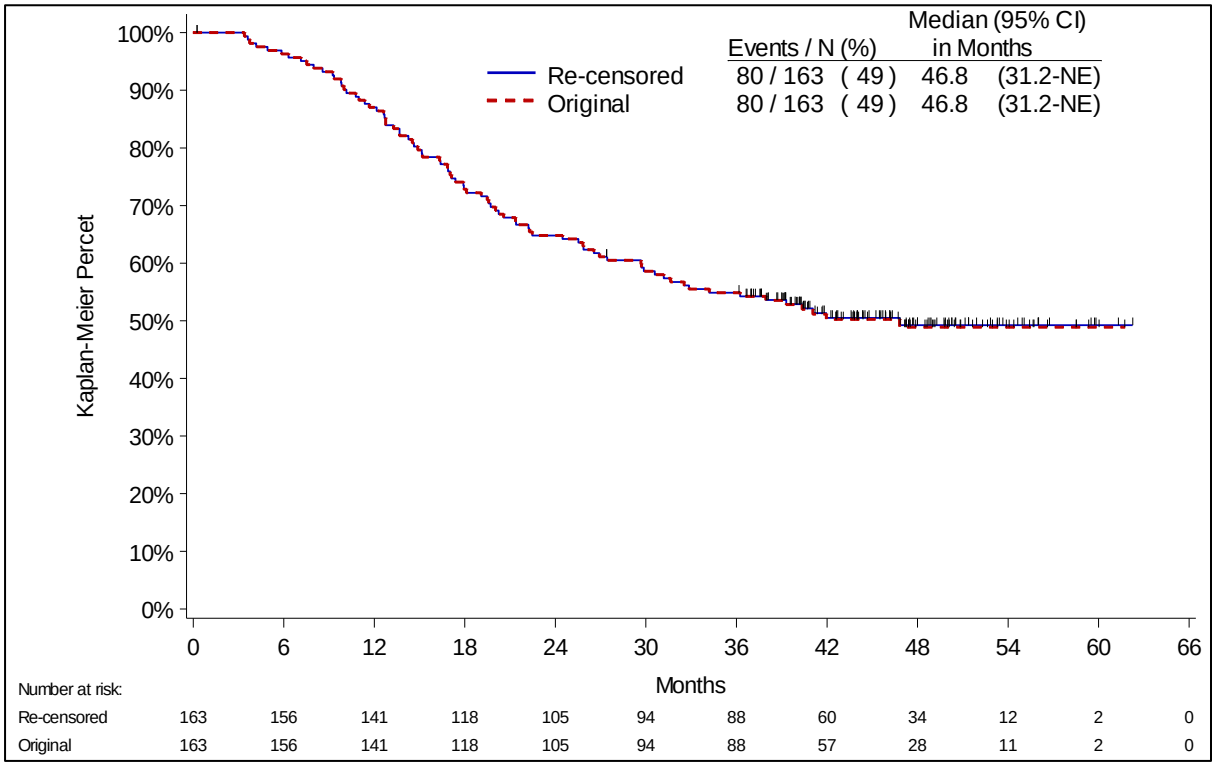
For PFS, the Kaplan-Meier estimates diverge after about 6 months with higher PFS rates after re-censoring (Figure B-2). However, the difference observed is mainly because the new censoring times were not allowed according to the original definition of the PFS endpoint. For the original analysis, censoring 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

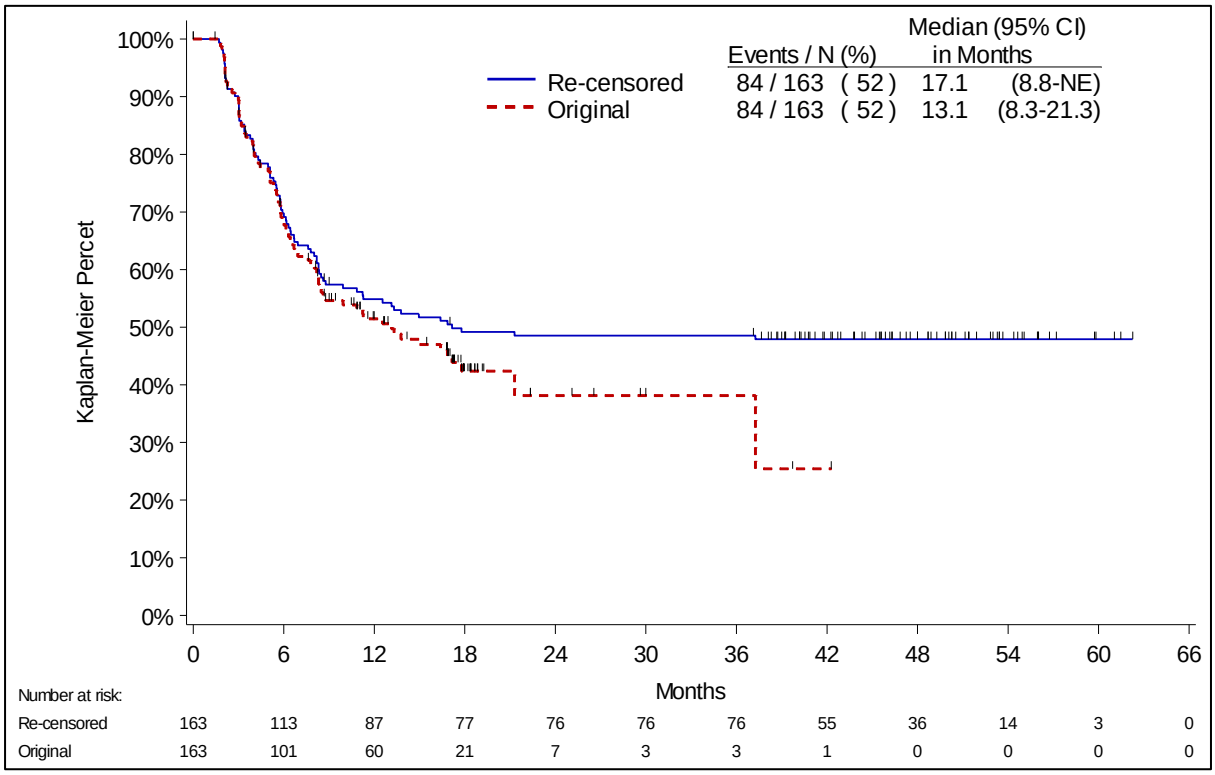
	Original censoring	Re-censoring as per ERG request
Mean OS (months)	33.1	33.1
Mean PFS (months)	19.0	21.4
Mean PPS (months)	18.3	18.3
ERG, Evidence Review Group; PFS, progression-free survival; PPS, post progression survival; OS, overall survival.		

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



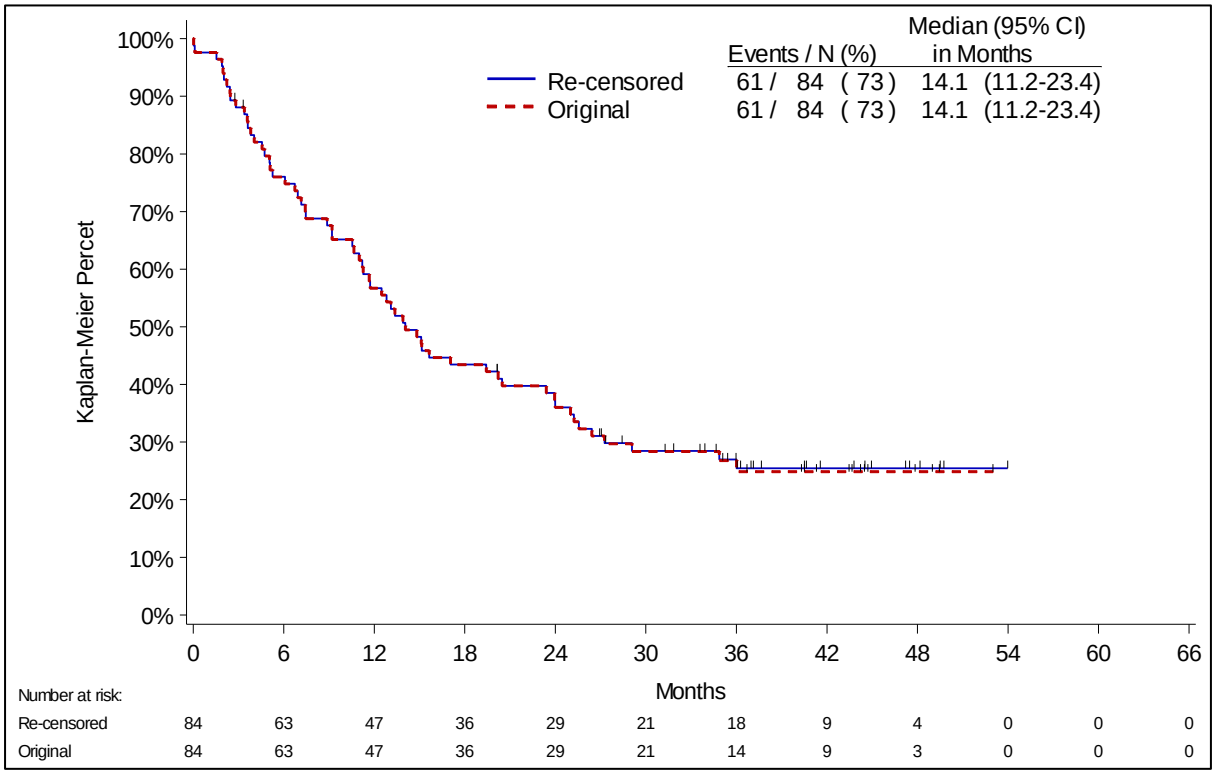
OS, overall, survival; T-VEC, talimogene laherparepvec.

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.

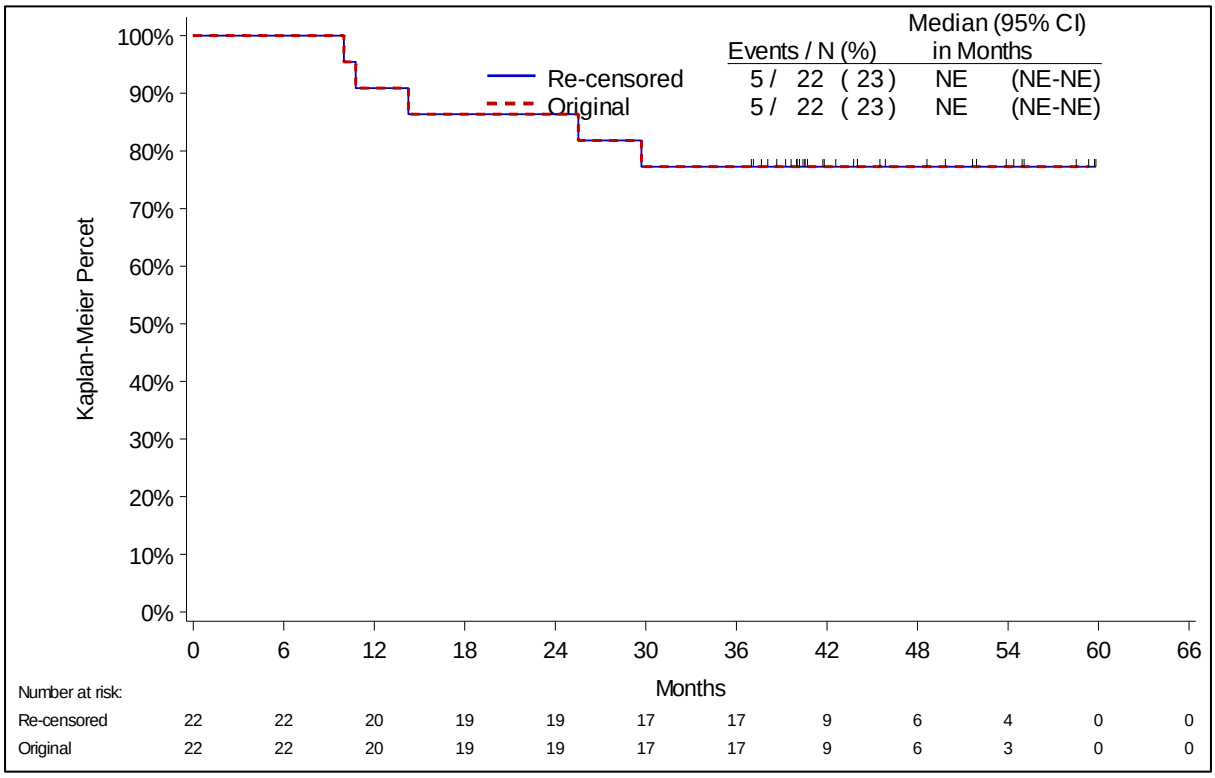
Similar analyses were performed stratified by disease stage and results were consistent with those for patients with stage IIIb-IVM1a combined. The differences in mean survival between the two censoring approaches are presented by stage in Table B-2. Kaplan-Meier estimates comparing the original censoring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

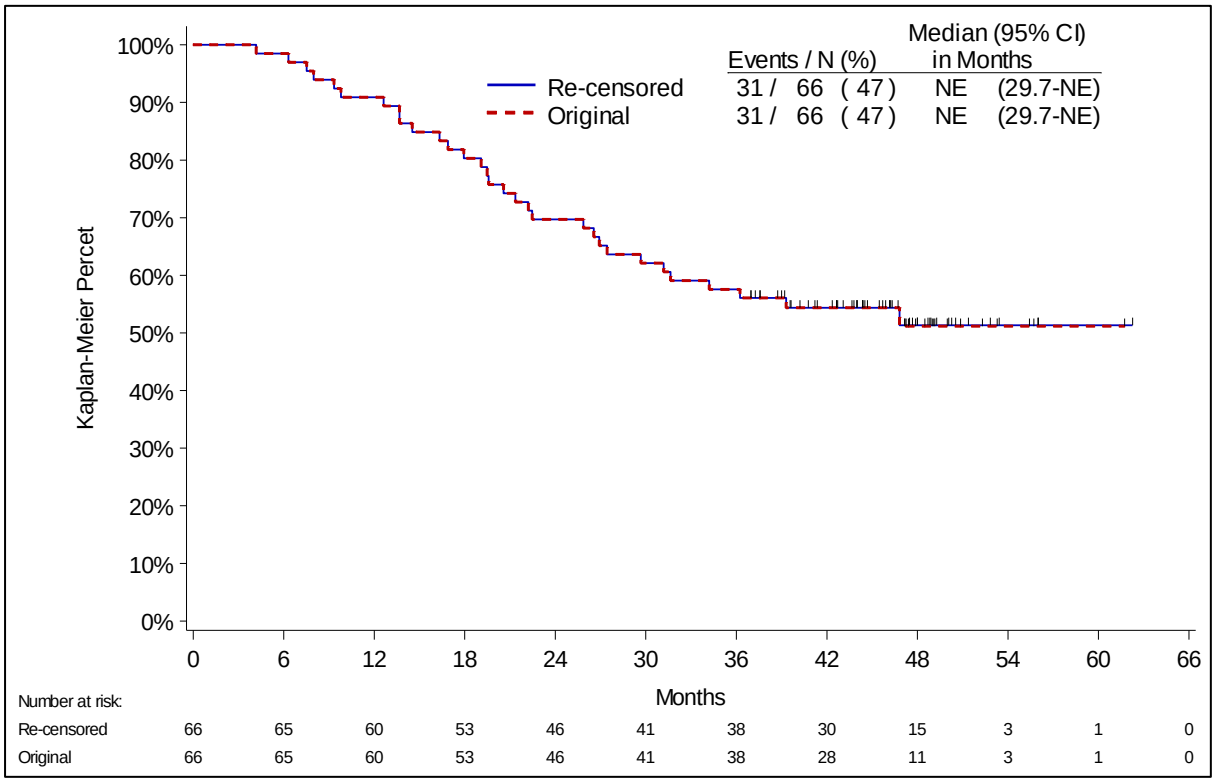
ERG, Evidence Review Group; PFS, progression-free survival; PPS, post progression survival; OS, overall survival.

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



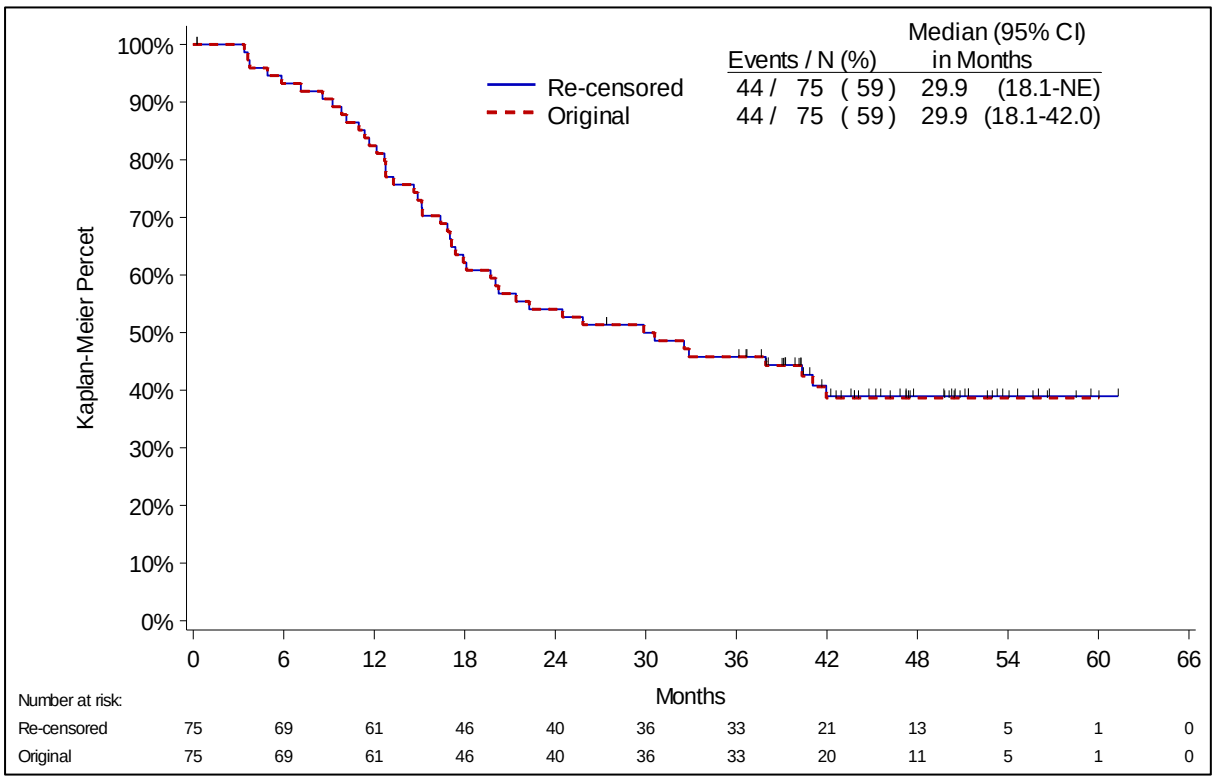
OS, overall, survival; T-VEC, talimogene laherparepvec.

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



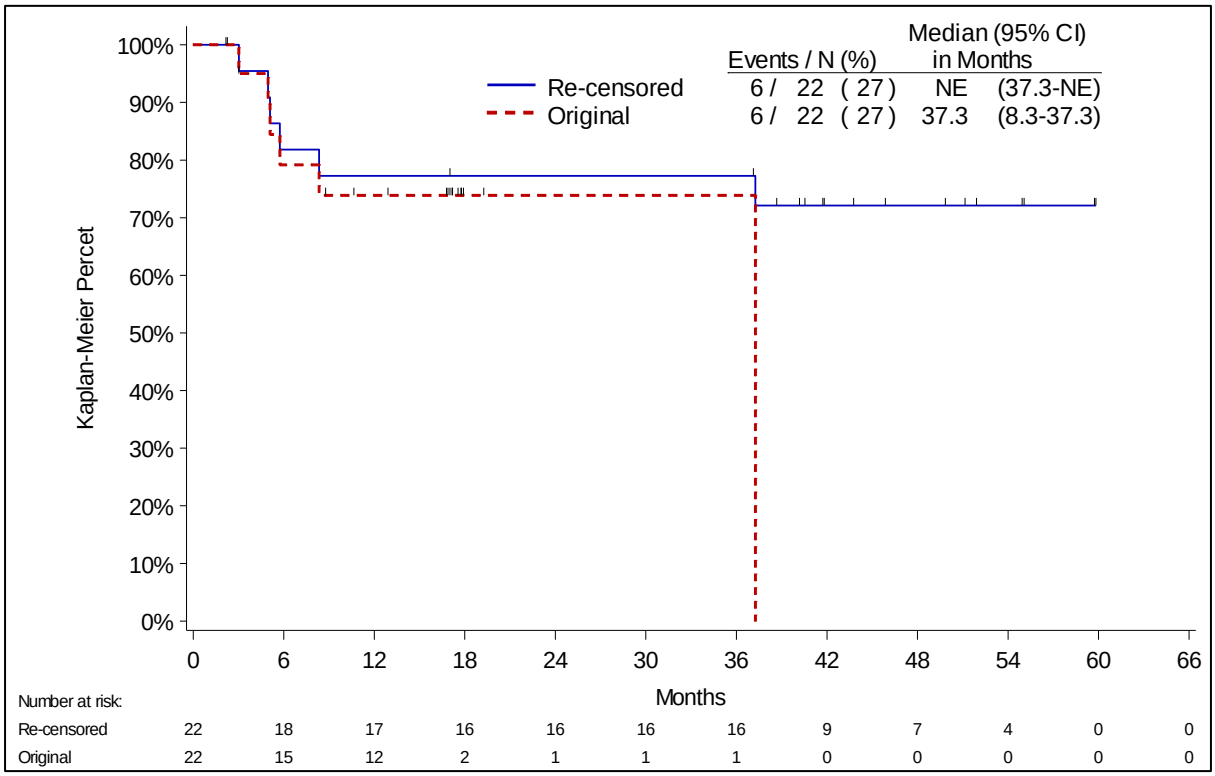
OS, overall, survival; T-VEC, talimogene laherparepvec.

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



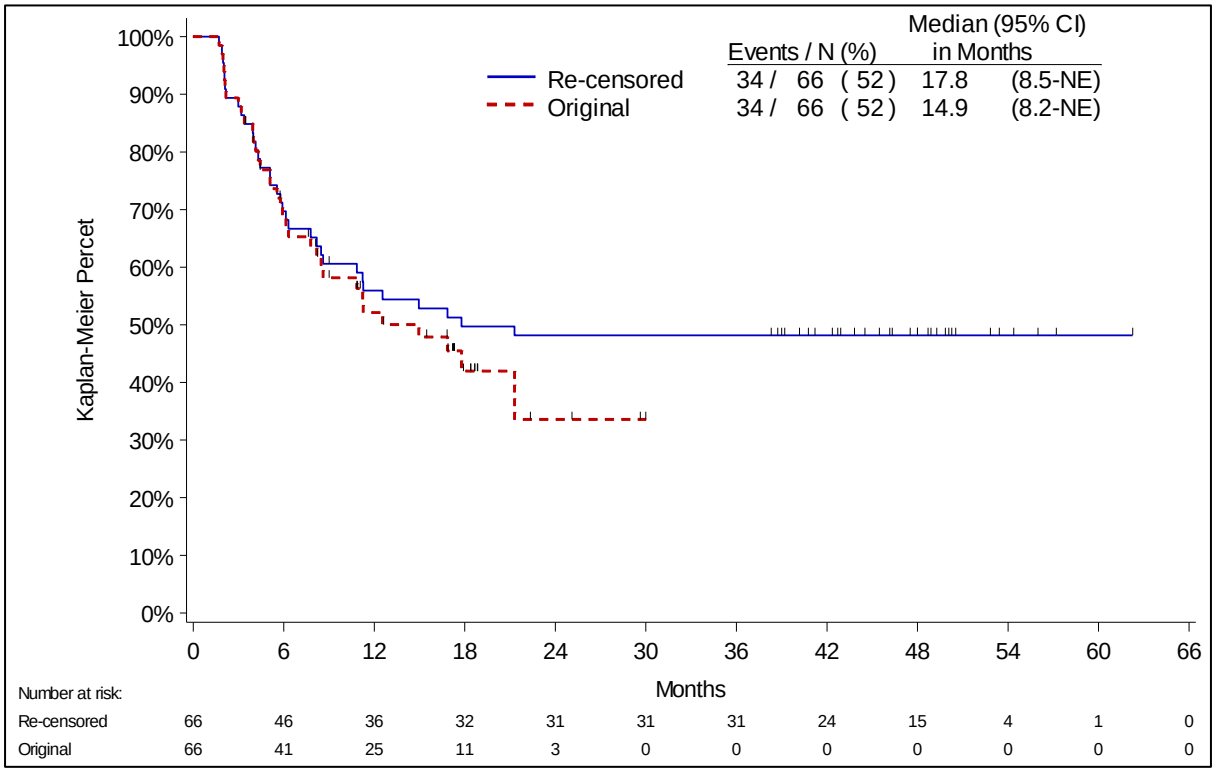
OS, overall, survival; T-VEC, talimogene laherparepvec.

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



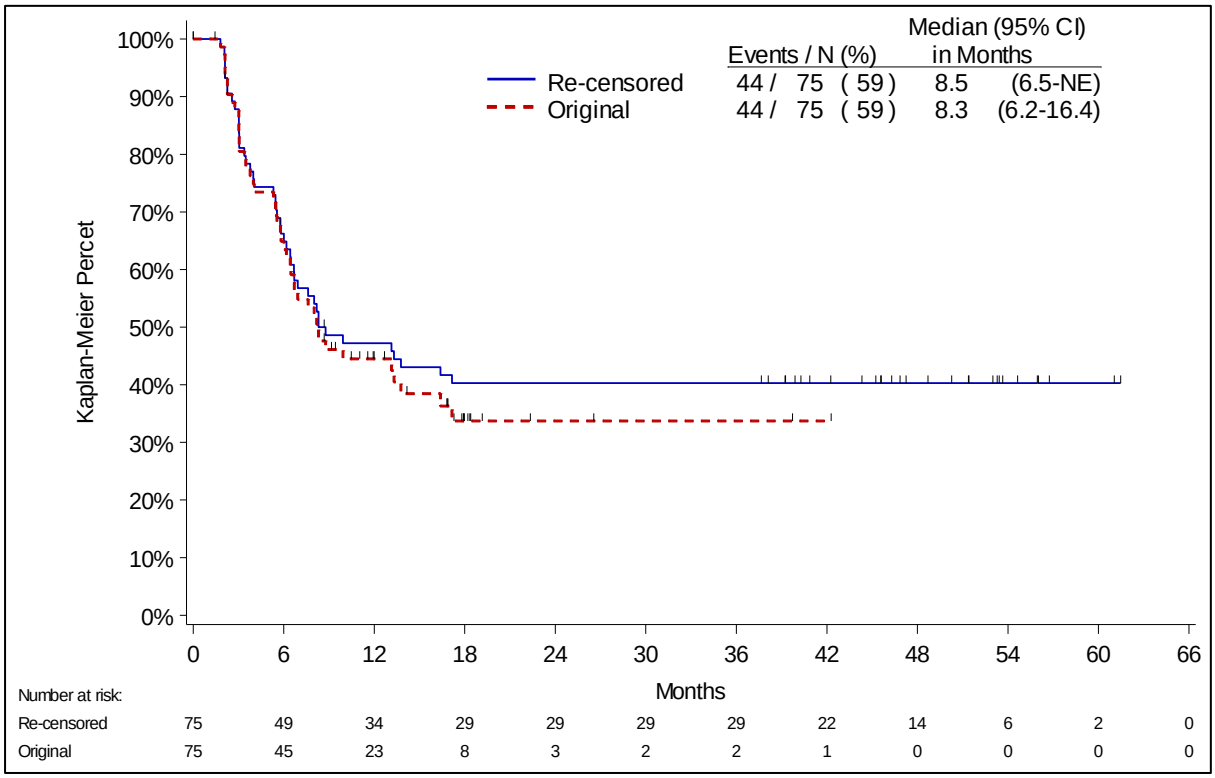
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

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



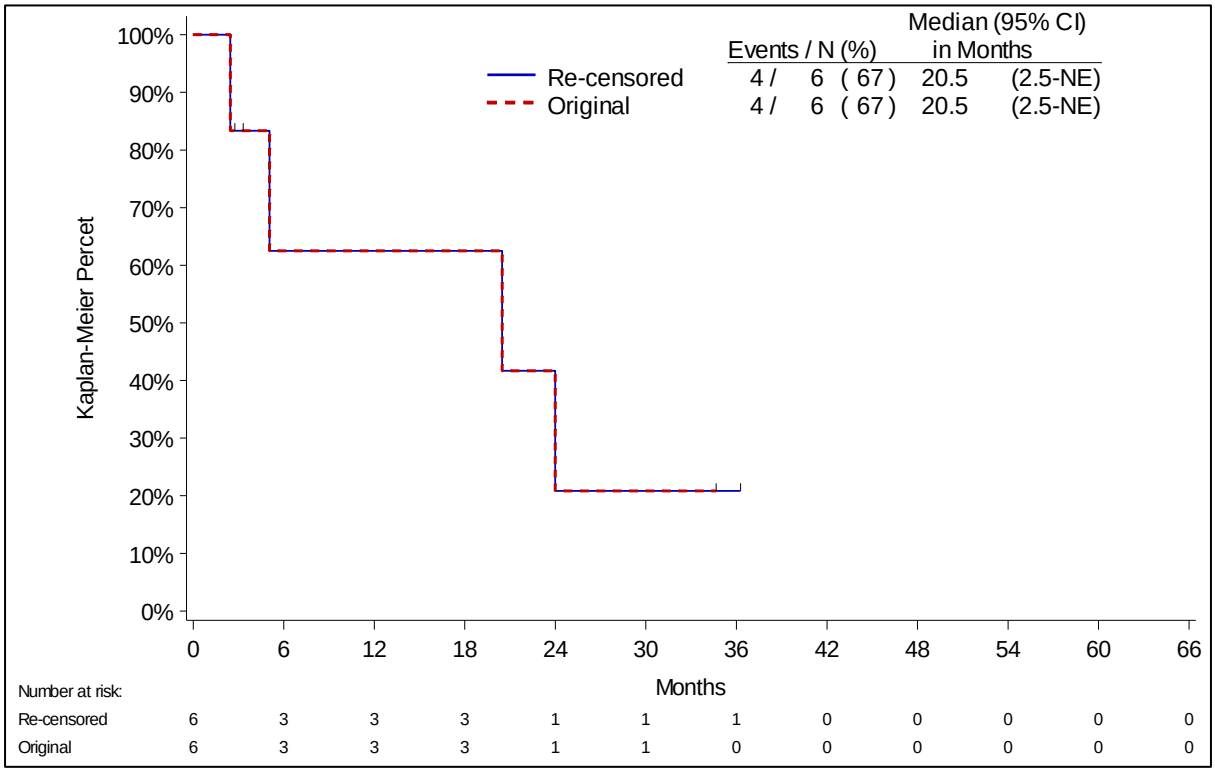
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

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



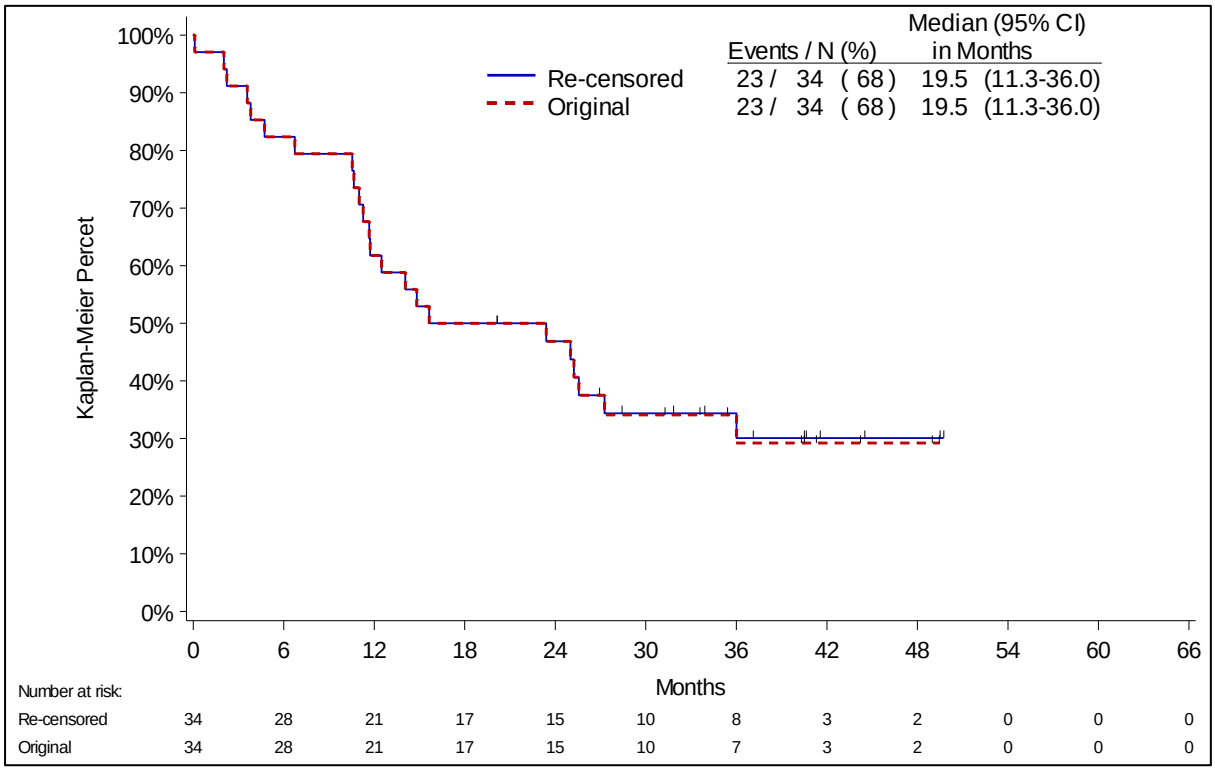
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

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



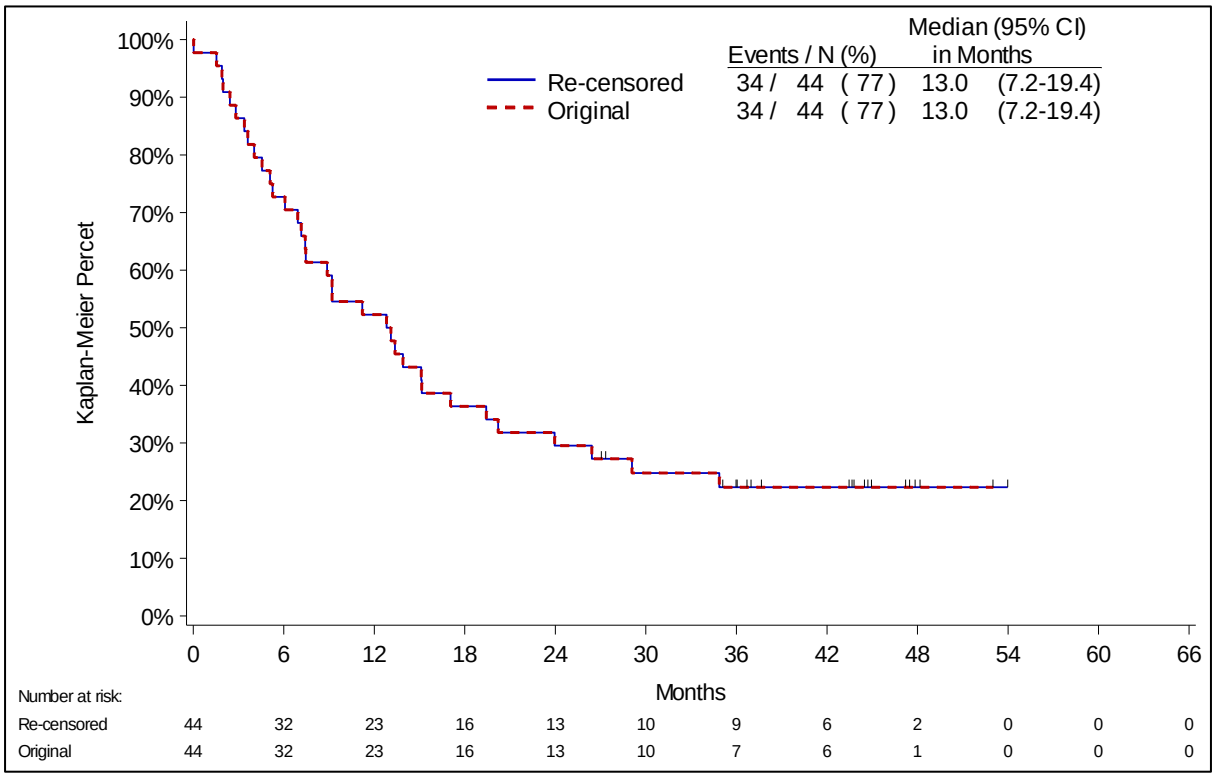
PPS, post progression survival; T-VEC, talimogene laherparepvec.

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:

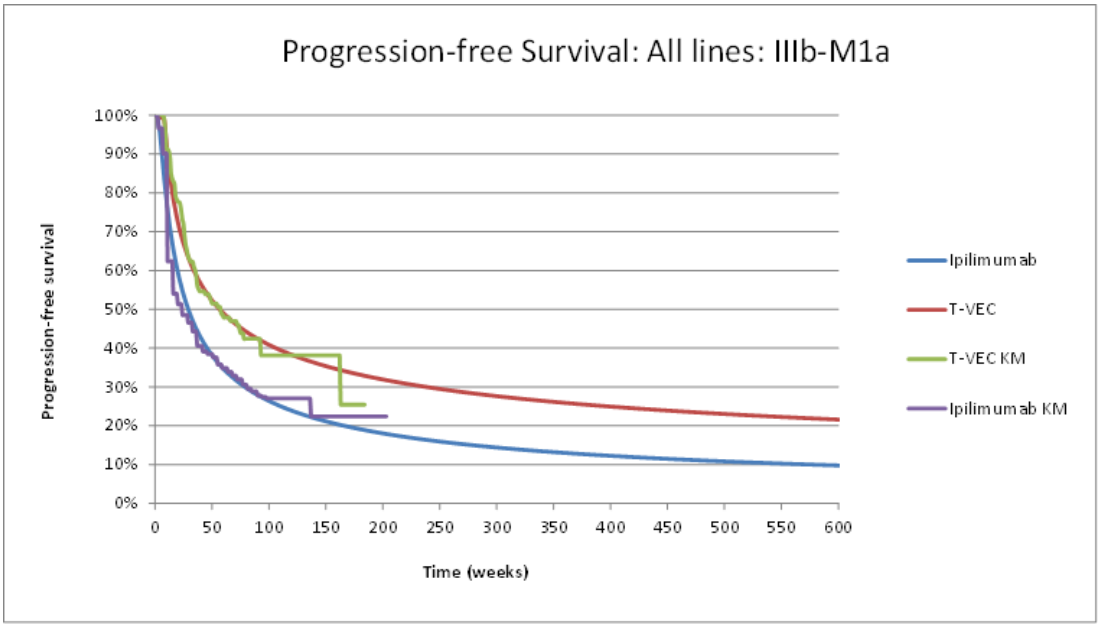
<u>B2 (Priority question)</u>. Application of Korn adjustments: Figures 5-30 and 5-32 indicate that in the T-VEC group the PFS estimates (and hence also the PPS estimates) are altered by the Korn adjustments, whereas OS is unaffected when either of the Korn adjustments are applied to the model. The ERG 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.

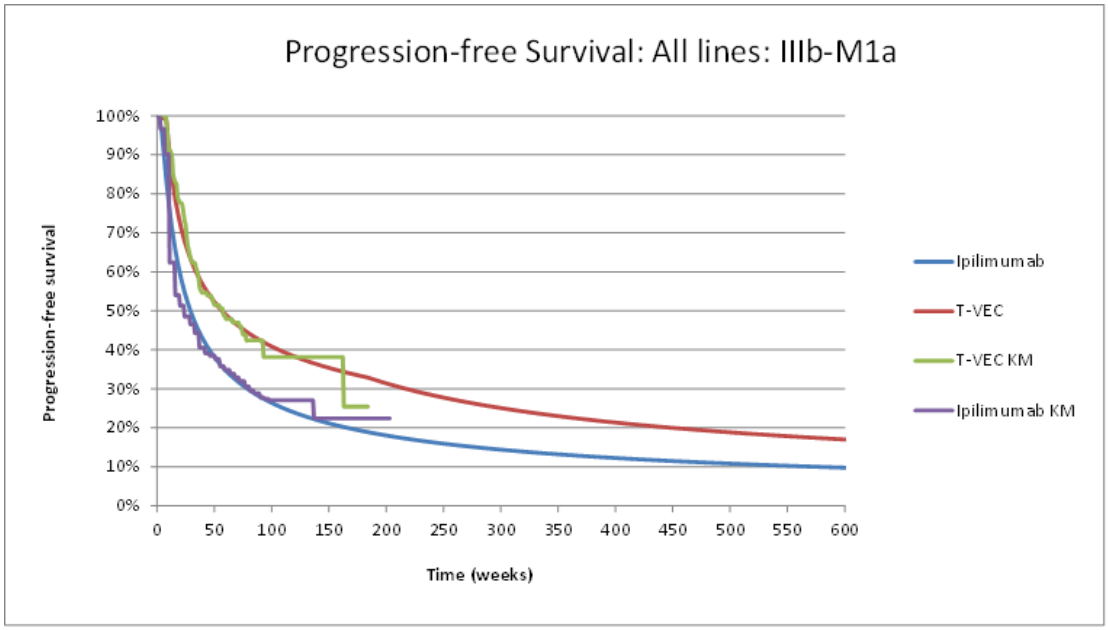
The impact of these assumptions on PFS is presented in Figure B-13 to Figure B-16 and Table B-3; results show that PFS estimates for T-VEC do not change when the assumption of similar hazards is not applied. Importantly the effect of the PFS adjustment on the incremental cost-effectiveness ratio (ICER)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



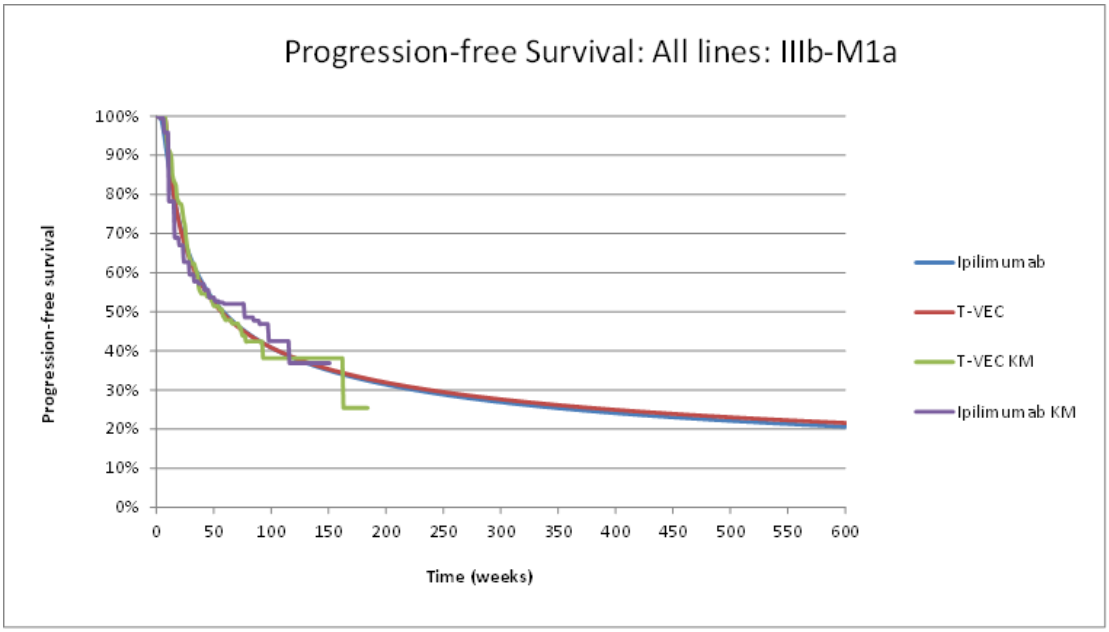
KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

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



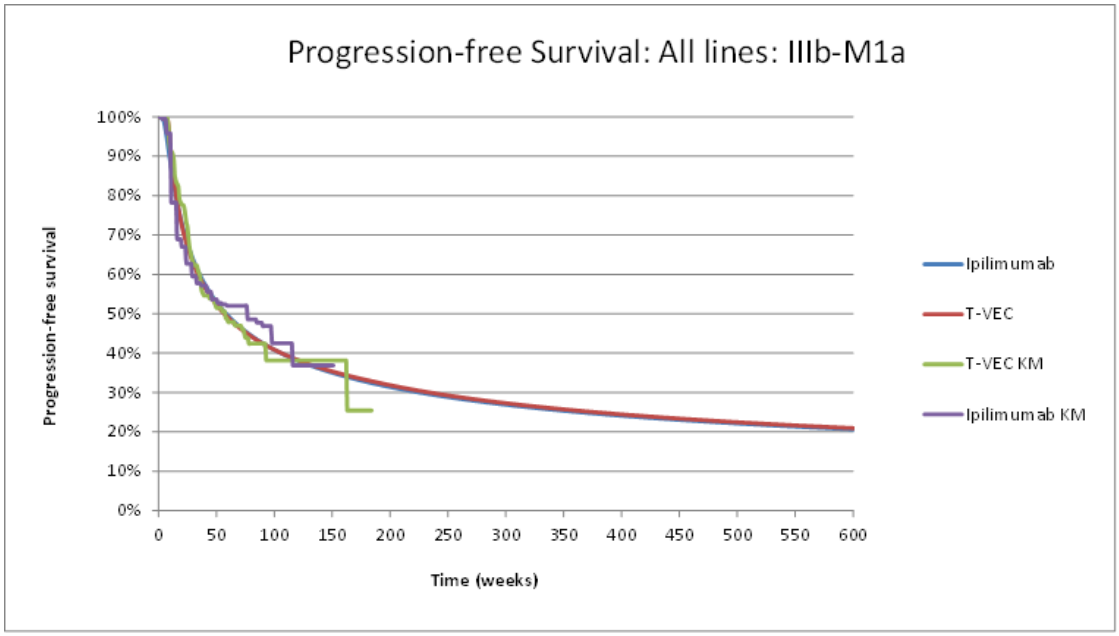
KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

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.

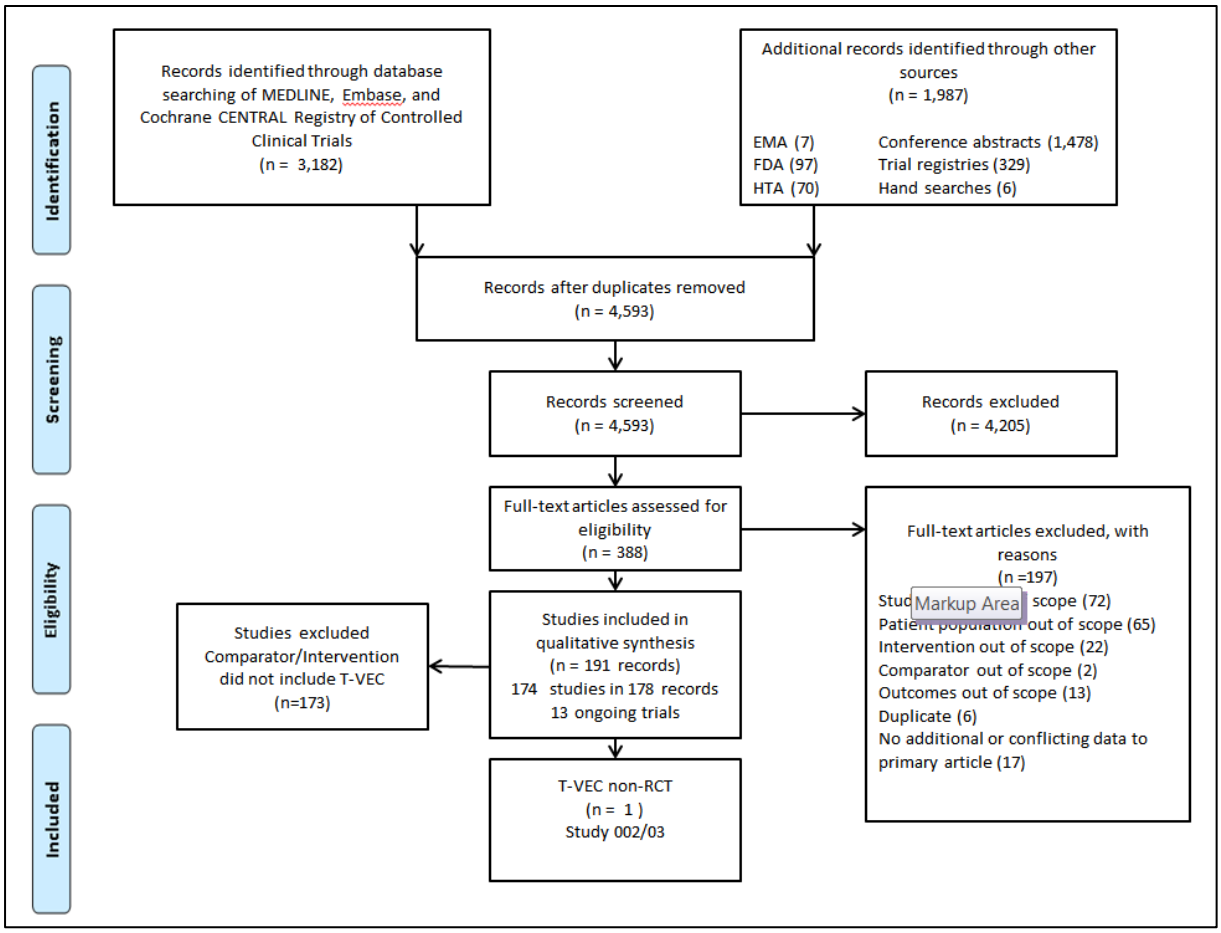
C2. Figure 3-1 includes a treatment pathway option for patients with BRAF V600 mutation positive disease starting with pembrolizumab followed by ipilimumab as a second-line option which is absent from Figure 3-2. Please clarify whether the company believes a treatment pathway starting with pembrolizumab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



References

Amgen (Data on file). Clinical study report: 005/05 Final Analysis 2015.

EMA. Summary of opinion (initial authorisation): Imlygic (talimogene laherparepvec) EMA/690530/2015: Committee for Medicinal Products for Human Use (CHMP), 2015.

Fink J, Born D, Chamberlain MC. Pseudoprogression: relevance with respect to treatment of high-grade gliomas. *Curr Treat Options Oncol*. 2011;12:240-252.

Harrington KJ, Andtbacka R, Collichio F, et al. Disease characteristics, treatment outcomes and safety with talimogene laherparepvec (T-VEC) vs GMCSF in patients with Stage IIIB-IVM1a melanoma in OPTiM 2015.

Hartung J, Knapp G, Sinha BK. Statistical meta-analysis with applications. John Wiley & Sons. ISBN 978-0-470-29089-7. 2008.

Hodi FS, O'Day SJ, McDermott DF, Weber RW, al e. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine*. 2010;363:711-723.

Kaufman H, Andtbacka RH, Collichio F, et al. Durable Response (DR)-Associated benefits in patients with unresected stage IIIB-IV melanoma treated with talimogene laherparepvec or GM-CSF in OPTiM. Poster presented at Society for Melanoma Research Meeting, San Francisco, 18-21 November. 2015.

Korn EL, Liu PY, Lee SJ, 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;26:527-534.

NICE TA319. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. June 2014. Available from http://www.nice.org.uk/guidance/TA319. Accessed 8 December 2015. 2014a.

NICE TA319. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD). June 2014. Available from http://www.nice.org.uk/guidance/ta319/resources/melanoma-previously-untreated-unresectable-stage-iii-or-iv-ipilimumab-id74-evaluation-report2. Accessed 10 December 2015. 2014b.

Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364:2517-2526.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.

List of Appendices

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Association of Skin Cancer Specialist Nurses (BASCSN)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify) Chair of BASCSN

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The BASCSN is broadly supportive of the approval of talimogene laherparepvec as another option in selected patients who have benefited in clinical trials.

Our members (skin cancer specialist nurses) have had limited experience with the drug (in clinical trials) and are not able to comment more fully on its efficacy or potential place in the management of melanoma.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation THE INSTITUTE OF CANCER RESEARCH

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? NO
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

THE EUROPEAN APPROVAL IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. I WILL CONFINE MY COMMENTS TO THAT SUBSET OF PATIENTS.
CURRENT NHS TREATMENT FOR THIS GROUP INCLUDES LOCAL PALLIATIVE SURGERY, ISOLATED LIMB PERFUSION, SYSTEMIC CHEMOTHERAPY (DACARBAZINE SINGLE AGENT, DACARBAZINE PLUS CISPLATIN, OR CARBOPLATIN PLUS PACLITAXEL), IMMUNOTHERAPY (IPILIMUMAB/NIVOLUMAB/PEMBROLIZUMAB) OR TARGETED DRUGS (BRAF INHIBITION +/- MEK INHIBITION).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

THE EUROPEAN APPROVAL IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. THIS GROUP APPEARED TO DERIVE GREATEST BENEFIT IN THE PHASE III OPTiM STUDY.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

USE OF THIS TECHNOLOGY IS LIKELY TO BE RESTRICTED TO SPECIALIST HOSPITAL UNITS WITH EXPERIENCE OF USING ONCOLYTIC IMMUNOTHERAPIES.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NOT CURRENTLY USED OUTSIDE OF CLINICAL TRIALS.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

THE APPROVED INDICATION IN EUROPE IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. THIS CAME FROM THE PHASE III OPTiM TRIAL IN WHICH THIS GROUP OF PATIENTS WAS SEEN TO DERIVE THE GREATEST DEGREE OF BENEFIT.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

T-VEC IS ASSOCIATED WITH VERY LITTLE LOCAL AND SYSTEMIC TOXICITY. IN THIS REGARD, IT COMPARES FAVOURABLY WITH OTHER LOCAL (SURGERY/ILP) OR SYSTEMIC TREATMENTS. ADMINISTRATION INVOLVES INTRATUMOURAL INJECTION – SOMETIMES WITH THE NEED FOR ULTRASOUND GUIDANCE. THERE ARE PRACTICAL CONSIDERATIONS REGARDING THE INTRATUMOURAL INJECTIONS – WITH A NEED FOR TRAINING. PATIENT ACCEPTABILITY IS VERY HIGH.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NO SPECIFIC COMMENTS.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

USE OF THIS AGENT IN CLINICAL TRIALS IS REPRESENTATIVE OF NORMAL CLINICAL PRACTICE. AS SUCH THE AGENT WILL BE APPLICABLE IN NORMAL UK PRACTICE.
THE PRIMARY OUTCOME OF OPTiM WAS DURABLE RESPONSE RATE (DEFINED AS A RESPONSE LASTING AT LEAST 6 MONTHS THAT OCCURRED AT ANY TIME IN THE FIRST 12 MONTHS OF TREATMENT). THIS "SURROGATE MEASURE" HAS BEEN SHOWN TO CORRELATE WITH PROLONGED REMISSION, OVERALL SURVIVAL AND AVOIDANCE OF THE NEED TO START OTHER THERAPIES.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

THE SIDE EFFECT PROFILE IS VERY MILD (THE ONLY GRADE 3 TOXICITY THAT OCCURRED IN MORE THAN 2% OF PATIENTS WAS LOCAL CELLULITIS). ANALYSIS OF THE OPTiM DATA INCLUDED FAVOURABLE NUMBER NEEDED

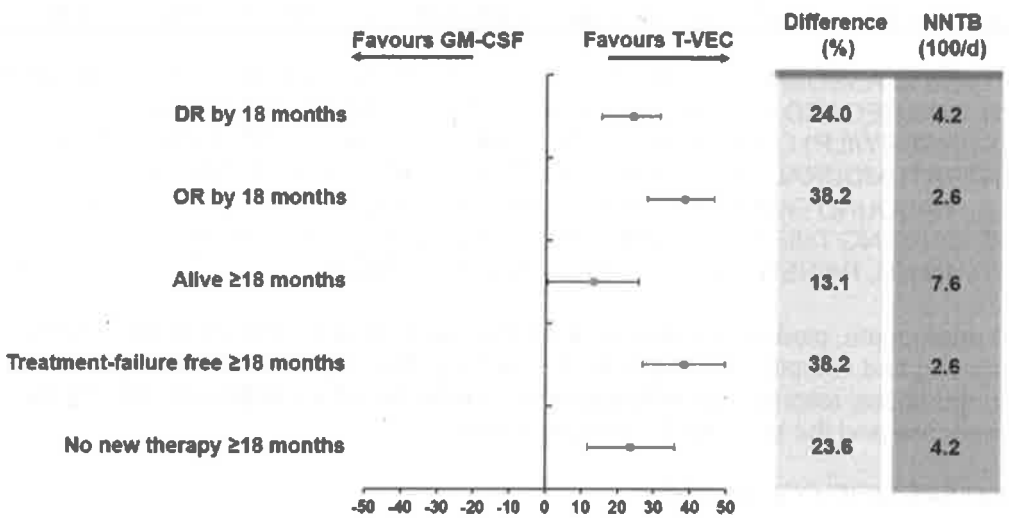
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

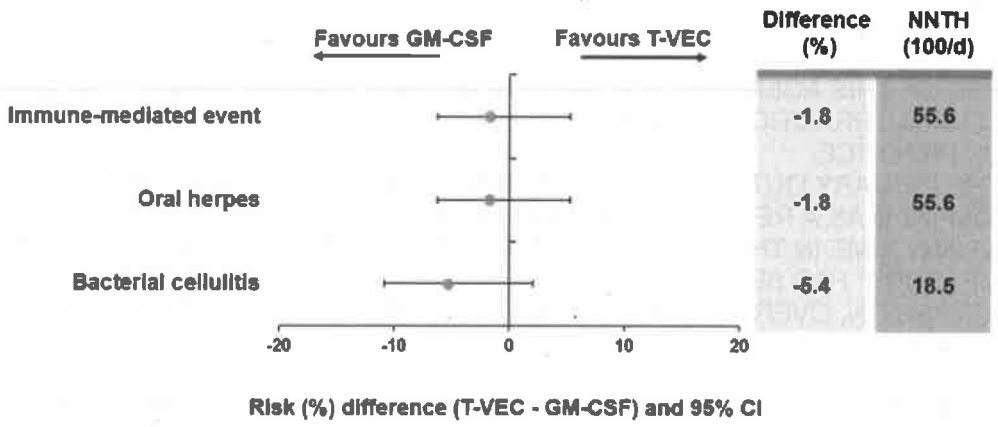
TO TREAT FOR BENEFIT AND NUMBER NEEDED TO TREAT FOR HARM ANALYSES (FIG 1 AND 2).

Figure 1. Benefit-risk analysis. (A) Benefits by 18 months (B) Risks by 18 months for the stage IIIB/C, IVM1a OPTiM subpopulation

A



B



CI, confidence interval; DR, durable response; GM-CSF, granulocyte-macrophage colony-stimulating factor; NNTB, number needed to treat to achieve a benefit; NNTH, number needed to treat to experience a harm; OR, overall response; T-VEC, talimogene laherparepvec.

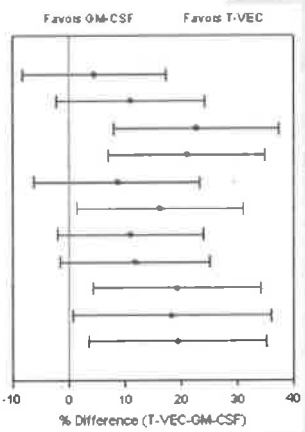
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

QUALITY OF LIFE ANALYSIS (FIGURE 3) CONFIRMS A FAVOURABLE EFFECT OF T-VEC OVER CONTROL ARM FOR MOST DOMAINS IN FACT-BRM.

Fig 3. Improvement in QoL assessed by FACT-BRM during treatment of T-VEC and GM-CSF in the stage IIIB/C, IVM1a OPTIM subpopulation (ITT)*

Subscale	N	Rate GM-CSF	Rate T-VEC	% Difference (95% CI)
Trial Outcome Index	207	23.4%	28.0%	4.5% (-8.2% - 17.3%)
FACT-BRM Total	215	26.9%	37.8%	11.0% (-2.2% - 24.2%)
Emotional Well-Being	197	31.6%	54.3%	22.7% (8.1% - 37.3%)
Functional Well-Being	193	25.8%	46.6%	20.8% (6.9% - 34.6%)
Physical Well-Being	130	18.2%	26.7%	8.6% (-6.2% - 23.3%)
Social/Family Well-Being	152	21.6%	37.6%	16.1% (1.3% - 30.8%)
Additional Concerns: Physical	186	20.0%	31.0%	11.0% (-2.0% - 23.9%)
Additional Concerns: Mental	189	22.0%	33.8%	11.8% (-1.5% - 25.2%)
QoL	157	22.4%	41.7%	19.2% (4.3% - 34.1%)
Pain	106	20.6%	38.9%	18.3% (0.7% - 36.0%)
Ability to Work	134	20.0%	39.4%	19.4% (3.5% - 35.2%)



CI, confidence interval; FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; GM-CSF, granulocyte-macrophage colony-stimulating factor; QoL, overall quality of life; T-VEC, talimogene laherparepvec.

*Scores from unscheduled visits were not included. A patients is considered evaluable for a domain if baseline score is not the best score and there is at least one post-baseline score. TOI and total improvements are defined as ≥5-point score increase from baseline with a ≥1 cycle duration. QoL, pain and work improvements are defined as ≥1-point score increase from baseline with a ≥1 cycle duration.

THERE HAS BEEN NO "ROUTINE CLINICAL PRACTICE". THEREFORE, NO OTHER ADVERSE EFFECTS HAVE COME TO LIGHT.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

NO CONCERNS

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
NO CONCERNS

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

NO CONCERNS

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation
Southampton University Hospitals NHS Foundation trust and University of Southampton

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- consultant Medical oncologist
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Metastatic malignant melanoma (MMM) is a condition, which remains fatal in the majority of patients. Recent clinical data have led to the approval of antic-CTLA4 (Ipilimumab) and anti-PD1 antibodies (Nivolumab, pembrolizumab) in the treatment of metastatic malignant melanoma. While these drugs have led to a significant improvement in outcome and the possibility of cure in some patients under 50% fall into this group. Chemothearpy plays no role in the management of metastatic malignant melanoma. Targeted therapies with BRAF inhibitors alone (Vemurafenib or dabrafinib) or in combination with MEK inhibitors improve survival in the ~40% of patients with cutaneous melanoma who have a mutation in the BRAF gene. They however do not offer cure but only palliative extension of live.
There is an urgent need to improve treatment options for patients with melanoma.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with MMM who have no visceral involvement, who have no brain involvement and who have normal LDH have per se a better outcome (M1a, M1b disease) compared to patients who have one or more of these high risk features. Nonetheless the overall outcome is that the majority of these patients die of their MMM.

This is the type of melanoma, in which the clinical Phase III trial data support the use of and benefit for patients by using **Talimogene laherparepvec.**
There is little risk from the technology to the patient, the injections are given into the injectable cancer lesions and therefore the risk is mainly from the need to physically deliver the **Talimogene laherparepvec** by injection.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

It should be used in a specialist oncology unit and managed and prescribed by an oncologist experienced in the use of immunotherapies.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The Technology is not currently available to patients with MMM.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline* and the specific evidence that underpinned the various recommendations.

No formal guidance exists with respect to this technology.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology will be easy to use but is time consuming (need to repeatedly inject tumour lesions). There is the need to discard of any clinical waste as GMO waste.
There is no alternative treatment – the treatment is first in class. It is expected that data will emerge over time of the use of this technology with anti-PD1 and anti-CTLA4 antibodies and that this combination may offer future potent further benefit for patients.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The injections are stopped if there is lack of clinical benefit. Globally speaking this would be progression in visceral organs or progression of injected sites of disease.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I believe that the clinical trials evidence reflects clinical practice including that in the UK. It is however a small portion of all MMM that would be suitable for this technology.
Local disease control, distant disease control (by stimulating an immune response that can attack non-injected lesions) and prevention of systemic disease progression are most likely benefits and these were measures in the published data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The injections are well tolerated. It is unlikely that any new adverse events will emerge in clinical practice.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not believe that there is any likelihood that this appraisal will affect equality of opportunity, cause unlawful discrimination or impair good relations to or between people with particular protected characteristics and others.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None identified

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I think that given the relatively small number of patients for whom this technology would be beneficial, it is unlikekly that there will be significant resource implications.

However specific training will have to be provided to the clinical teams for the appropriate management of the release and injection of the technology and the disposal of any waste related to the technology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you
Your name:
[redacted]

Name of your organisation
The Christie NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? X
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Not an employee of but board member of British association of skin cancer nurses
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Metastatic melanoma is treated with a variety of treatments depending on Molecular mutation status and aggressiveness of disease. There are, perhaps minor differences of opinion regarding the order in which certain treatments are given and the duration of treatment in specific cases but, overall there is consensus among the leading clinicians in this area of cancer medicine. Melanoma patients should be managed in specialist centres.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
The prognosis of a melanoma patient is variable. This technology would be considered for patients who had no BRAF mutation and or disease which was refractory to or progressing on immunotherapy or targeted therapy.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
This technology should only be used in specialist centres with experience of treating metastatic melanoma and managing patients on novel therapies. There would need to be additional training in the administration of the drug. If patients' wounds need dressing by district nurses they may need additional training about safe disposal of dressings.
There is unlikely to be a need for any additional input from other health care professionals.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
This technology has not been available except as part of a clinical trial.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
I am not aware of any current clinical guidelines with this treatment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
This technology will be more difficult to give as the drug is injected directly into the tumour and this will need specific training. There will be a finite number of people who are experienced in administering the drug in any one institution.
. There should be no change in the amount of blood tests, clinic visits or CT scanning. Overall this drug is very well tolerated and unlikely to need additional resources to manage toxicity.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
None known

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

I was not involved in the clinical trials of this technology. Therefore I have little knowledge of how the trials were conducted.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Overall side effects are few and easily managed. Toxicity is unlikely to affect quality of life or management.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

None of the above

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NA

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
There would be some additional training in administration and understanding of a genetically moderated substance. From my understanding of the trials the drug should be administered in a private room which is cleaned after drug administration, I am not sure if this will be necessary post licence. There may be some implications for pharmacy re being able to store the drug correctly at the correct temperature.
Individual trusts would have to negotiate whether the drug was drawn up by pharmacy or the person administering the agent. I am aware that this varied in the clinical trials.
Relevant patient/carer information would have to be produced but, again this would be minimal.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name:
Name of your nominating organisation: Melanoma UK
Do you know if your nominating organisation has submitted a statement?

☐ **Yes** ☐

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ ☐ **No**

- a carer of a patient with the condition?

☐ ☐ **No**

- a patient organisation employee or volunteer?
-

☐ **Yes** ☐

Do you have experience of the treatment being appraised?

☐ ☐ **No**

If you wrote the organisation submission and do not have anything to add, tick here ☒ (If you tick this box, the rest of this form will be deleted after submission.)

2. *Living with the condition*

What is your experience of living with the condition as a patient or carer?

Speaking regularly with advanced melanoma patients there is no doubt that this is a very serious and debilitating disease. Advanced Melanoma is a brutal disease and a patient living with the disease without treatment can expect to survive between 3-9 months without treatment. The disease disproportionally affects young people and in an advanced stage, this can mean a young patient is looking at a very limited life expectancy and all the trauma that that brings.

3. *Current practice in treating the condition*

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment in advanced melanoma has always been a complicated area of medicine. Up until the last few years, advanced melanoma was notoriously difficult to treat. Patients and clinicians had limited treatment options. The treatment being appraised today has been seen as a step change in the treatment of advanced patients. Patients have reported reduction in tumours and minimal side effects. The side effects of some treatments are debilitating and this is a very important issue for patients and carers. This treatment is of particular interest to patient who are presenting with tumours that are visible to the outside world. We have had reports of patients who are desperate to be considered for this treatment.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

As a patient advocacy group we are aware of other treatments in advanced melanoma. Not all of them are appropriate or suitable for all patients and each treatment has its own advantages and disadvantages. Given that we only have anecdotal evidence from patients as to the efficacy of these treatments, it is really for the patient expert to advise on acceptability.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Improved prospect of quality, long term survival. Evidence of improved patient outcomes and experience to Melanoma UK's knowledge.

Patients have been made aware of instances of better progression free survival which is being seen compared to other treatments and standard of care. Patients understand that there may be a reasonable side effect profile which is important to them.
Targets an area of high unmet need. Melanoma is on the increase in the UK and leading clinicians have made it clear that there is a desire to be able to offer as many alternative treatments as possible as early as possible in the treatment pathway. This is not just limited to clinicians – patients and carers have a strong appetite to have access to as many treatments as possible.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Dealt with above

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

There will always be the risk of adverse side effects or the treatment not being suitable for the treatment, but just as with other melanoma treatments, patients are anxious for this to be another option.

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ **No**

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. *Other issues*

Do you consider the treatment to be innovative?

☐ **Yes** ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

There is the suggestion that this treatment can have a dual effect - killing cancer cells directly and harnessing the immune system against them.

Is there anything else that you would like the Appraisal Committee to consider?

We say similar things every time we appear before the committee, but to reiterate : until very recently, advanced melanoma patients have had little hope of long term survival. This is another new treatment which is showing such promise and patients are anxious that there is another treatment made available to them. Melanoma is a brutal disease and patients are desperate for any treatments that might help them to be able to function at a proper level.,

10. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

- Meets the need of advanced melanoma patients
- Reasonable side effect profile
- Another option for patients and clinicians
-
-

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/04

Completed 19th January 2016

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Talimogene laherparepvec for treating metastatic melanoma [ID508]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors:

Nigel Fleeman, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Adrian Bagust, Professor (Health Economic Modelling), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Marty Richardson, Research Fellow (Medical Statistician), LR*i*G, University of Liverpool

Ashma Krishan, Research Fellow (Medical Statistician), LR*i*G, University of Liverpool

Angela Stainthorpe, Research Associate (Health Economic Modelling), LR*i*G, University of Liverpool

Ahmed Abdulla, Research Associate (Health Economic Modelling), LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Lindsay Banks, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool

Miranda Payne, Consultant in Medical Oncology, Oxford University Hospitals NHS Trust, Oxford

Correspondence to: Nigel Fleeman, Research Fellow, Liverpool Reviews & Implementation Group, University of Liverpool, Room 2.09, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 19th January 2016

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/206/04.

Declared competing interests of the authors: None.

Acknowledgements: The authors would like to thank Dr Ernie Marshall who provided feedback on draft versions of the report and answered questions on comparators and disease stage.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Fleeman N, Bagust A, Boland A, Beale S, Richardson M, Krishan A, Stainthorpe A, Abdulla A, Kotas E, Banks L, Payne M. Talimogene laherparepvec for treating metastatic melanoma [ID508]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2014

Contributions of authors:

Fleeman N	Project lead, critical appraisal of clinical evidence, drafted background, critique of decision problem and clinical results sections and supervised the final report
Bagust A	Checking and validation of the economic model and critique
Boland A	Critical appraisal of the clinical and economic evidence
Beale S	Critical appraisal of the clinical and economic evidence
Richardson M	Critical appraisal of the statistical evidence
Krishan A	Critical appraisal of the statistical evidence
Stainthorpe A	Critical appraisal of the economic evidence
Abdulla A	Critical appraisal of the economic evidence
Kotas E	Cross checking of the submission search strategy
Banks L	Critical appraisal of the submission
Payne M	Clinical advice and critical appraisal of the clinical sections of the submission

All authors read and commented on draft versions of the ERG report.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSC	best supportive care
CEAC	cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CS	company submission
CSR	clinical study report
DR	durable response
DRR	durable response rate
DTIC	dacarbazine
EAC	Endpoint Assessment Committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACT-BRM	Functional Assessment of Cancer Therapy-Biologic Response Modifier
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
FDA	Food and Drug Administration
GM-CSF	granulocyte-macrophage colony-stimulating factor

HR	hazard ratio
HRQoL	health-related quality of life
HRU	health resource utilisation
HSV-1	herpes simplex virus type-1
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
NMA	network meta-analysis
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDr	clinically relevant progressive disease
PFS	progression-free survival
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCT	randomised controlled trial
RMP	risk management plan
SAE	serious adverse event
SAEOSI	serious adverse event of special interest
TSAP	trial statistical analysis plan
TTF	time to treatment failure
T-VEC	talimogene laherparepvec

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Amgen Limited in support of the use of talimogene laherparepvec (Imlygic®) (hereafter referred to as T-VEC) to treat patients with non-visceral metastatic melanoma.

1.1 Critique of the decision problem in the company's submission

The intervention specified in the NICE scope is T-VEC. It has been recognised by the European Medicines Agency (EMA) as a novel, first-in-class oncolytic immunotherapy treatment. The company estimates that, if recommended by NICE, 728 patients in England would be eligible for treatment with T-VEC in 2015.

The population specified in the NICE scope is adults with stage IIIB to stage IV melanoma. A positive opinion for the granting of a marketing authorisation has been issued by the Committee for Medicinal Products for Human Use and is awaiting approval by the European Commission expected in [redacted]. It is anticipated that the licence will be for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease. However, as T-VEC is administered by intralesional injection, its use will be restricted to patients whose melanoma is considered injectable, i.e. there must be cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance.

The following comparators are specified in the NICE scope: ipilimumab, vemurafenib and dabrafenib. Unfortunately, none of these drugs has been studied in trials comprising only patients with non-visceral metastatic stage IIIB to stage IV M1a melanoma or in trials where these patients are a specified subgroup. Ipilimumab is considered by the company to be the primary comparator to T-VEC and vemurafenib and dabrafenib are not evaluated in the company submission (CS). However, with NICE's recent recommendation that pembrolizumab should be made available through the NHS as a treatment for some patients with metastatic melanoma, the ERG considers that, in future, all patients who are currently offered first- or second-line treatment with ipilimumab will now be offered pembrolizumab (if they have not already received it).

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope: overall survival (OS), progression-free survival (PFS), tumour response rate, adverse events

(AEs) of treatment and health-related quality of life (HRQoL). These are all outcomes that are commonly measured in metastatic melanoma drug trials. In addition, durable response rate (DRR) was also reported as the primary outcome in the OPTiM trial from which the majority of evidence for T-VEC is derived; DRR is a non-validated, albeit a clinically relevant, endpoint. The OPTiM trial reported time to treatment failure (TTF) instead of PFS since patients were permitted to continue to receive treatment despite showing evidence of disease progression with T-VEC.

1.2 Summary of clinical effectiveness evidence submitted by the company

Evidence for the relative efficacy of T-VEC was obtained from the OPTiM randomised controlled trial (RCT). Evidence from one Phase II non-RCT (Study 002/03) is also presented in the CS.

In the open label OPTiM trial patients with stage IIIB to stage IV M1c disease were randomised in a 2:1 ratio to receive either T-VEC (n=295) or granulocyte macrophage colony-stimulating factor (GM-CSF) (n=141). The anticipated licence for T-VEC is based on clinical data from a post-hoc analysis of a subgroup of these patients (n=249), namely patients with injectable non-visceral metastatic melanoma (i.e. stage IIIB to stage IV M1a disease). Post-hoc analysis refers to those in which the hypotheses being tested are not specified before any examination of the data. The results for this subgroup (final data cut) are:

- DRR by Endpoint Assessment Committee (EAC) assessment was higher in patients treated with T-VEC compared with GM-CSF (25.2% vs 1.2%; unadjusted odds ratio 28.6; [95% CI: 3.9 to 211.5]; p<0.0001)
- TTF by investigator assessment was longer in the T-VEC arm than in the GM-CSF arm (median 13.1 months vs 3.3 months; hazard ratio [HR]=0.28; [95% CI: 0.20 to 0.40]; p<0.0001)
- Overall tumour response rate by EAC assessment was higher in the T-VEC arm than in the GM-CSF arm (40.5% vs 2.3%, p<0.0001)
- At the final OS analysis, median OS gain was 25.3 months for patients in the T-VEC arm vs patients in the GM-CSF arm (median 46.8 months vs 21.5 months, unstratified HR=0.56; [95% CI: 0.40 to 0.79]; p=0.0008).

In patients with non-visceral metastatic disease treated with T-VEC, treatment-related Grade 3 to 5 AEs and treatment-related serious AEs (SAEs) were reported by 14% and 6% of patients respectively, and treatment emergent AEs leading to discontinuation were reported by 9% of patients. In the overall trial population, the most common AEs reported by patients receiving T-VEC were flu-like symptoms (90%) and injection-site reactions (42%).

HRQoL data were collected as part of the OPTiM trial using the Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM) questionnaire. Results show that, for the patients with non-visceral metastatic melanoma, in six of the 11 measures that were used the differences identified between trial arms reached statistical significance and favoured T-VEC.

Unlike the OPTiM trial, Study 002/03 did not include patients with stage IIIB melanoma and only included 23 patients with stage IIIC to stage IV M1a disease; an additional 27 patients had later stage disease. Relevant subgroup findings were not reported in the CS. Nevertheless, the company considers Study 002/03 provides supportive evidence for the effectiveness of T-VEC.

Despite undertaking a broad literature search, only the OPTiM trial was identified as being relevant to the decision problem. Furthermore, none of the comparators identified in the NICE scope has been studied in trials comprising only patients with non-visceral metastatic melanoma or in trials were patients with non-visceral metastatic disease are a specified subgroup. Therefore it was not possible for the company to construct a complete network that would determine indirect estimates of the clinical effectiveness of the comparators listed in the NICE scope to be determined. Furthermore, the company did not attempt to estimate the clinical effectiveness of vemurafenib or dabrafenib but did explore a number of different ways to obtain evidence for the efficacy of ipilimumab in patients with non-visceral metastatic melanoma. After considerable investigation, the company concluded that two methods could be used, the modified Korn model ("best case" findings) and the two-step Korn model ("worst case" findings). Both methods aim to adjust baseline characteristics so that patients who had received ipilimumab in two previous trials were comparable to those in the OPTiM trial. Results using the modified Korn model suggest T-VEC to be superior to ipilimumab, whilst results using the two-step Korn model suggest that T-VEC is at least comparable to ipilimumab in patients with non-visceral metastatic melanoma.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company's literature searches did not identify any studies, in addition to the OPTiM trial or Study 002/03, which included T-VEC (or GM-CSF) as either an intervention or comparator. Nor did they reveal any studies which assessed the efficacy of ipilimumab, vemurafenib or dabrafenib in patients with non-visceral metastatic disease. The ERG is not aware of any additional RCTs or non-randomised studies, which should have been included as part of the evidence base.

Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with stage IIIC to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England.

The ERG has concerns that the population considered in this STA is one that has been constructed following the results of a post-hoc analysis of data collected during the OPTiM trial. The ERG is particularly concerned that the disease trajectory of patients with stage III disease is likely to differ from that of those with stage IV M1a disease. Furthermore, the ERG considers that the OPTiM trial may be subject to bias due to limited blinding, a higher proportion of dropouts in the GM-CSF arm (particularly in the first few months of the trial), and the use of DRR as the primary endpoint. It is noted in the draft European Public Assessment Report (EPAR) that DRR is a new, clinically relevant, endpoint that is non-validated and is potentially prone to bias. However, the ERG does not consider that the potential sources of bias fully explain the improvements in efficacy in the T-VEC arm compared with the GM-CSF arm. The ERG notes that a further uncertainty, raised by the US Food and Drug Administration (FDA), relates to the size of lesions. The results of an FDA post-hoc analysis of the overall intention-to-treat population (i.e. including those with stage IV M1b and stage IV M1c disease) suggest that patients who had very small lesions (<1 cm^2) were more likely to respond to T-VEC than were the overall population (10.1%). The ERG further notes that evidence for the effectiveness of T-VEC treatment is not presented by line of therapy in the subgroup of patients with non-visceral metastatic disease.

Results from the OPTiM trial suggest that T-VEC's safety profile compares favourably with those of the comparator treatments detailed in the NICE scope. The ERG, however, notes that there are limited data to support the long-term safety of treatment with T-VEC.

Although HRQoL data collected as part of the OPTiM trial show that, in general, quality of life for patients receiving T-VEC was better than for those receiving GM-CSF, a substantial proportion of patients in the GM-CSF arm did not complete HRQoL assessments, suggesting that the HRQoL findings should be interpreted with caution.

For reasons highlighted in Section 1.5, the ERG does not consider the ipilimumab survival estimates generated by the company, using either the modified Korn model or the two-step Korn model to be reliable. It is, therefore, impossible to determine the relative clinical effectiveness of T-VEC compared with any of the comparators listed in the NICE scope.

1.4 Summary of submitted cost effectiveness evidence

To allow the cost effectiveness of T-VEC to be compared with that of ipilimumab, the company developed a de novo partitioned survival model. The model comprised three mutually exclusive health states: non-progressive disease, progressive disease and death. All patients entered the model in the non-progressive disease state. Variants of this model structure have been used in a number of previous STAs that have considered the cost effectiveness of treatments for patients with metastatic melanoma. The model has been developed in Microsoft Excel using a 1-week cycle length and the time horizon is set at 30 years. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in quality adjusted life years (QALYs). The model perspective is that of the UK NHS.

PFS for patients receiving T-VEC was based on OPTiM trial data for TTF and published sources. For patients treated with ipilimumab, two different PFS models were developed, depending on whether data from two ipilimumab trials were adjusted for differences in baseline characteristics between these trials and the OPTiM trial by using the modified Korn algorithm or the two-step Korn algorithm.

For patients receiving T-VEC, OS was modelled using a multi-phase approach that utilised both OPTiM trial data and published sources. The modelling of OS for patients treated with ipilimumab was a similar multi-phase approach, but with cut-points implemented at different times to those used to estimate OS for patients treated with T-VEC. Two different OS projections were developed for ipilimumab patients, depending on whether the modified Korn model or the two-step Korn model was used to adjust for differences in baseline characteristics between the two relevant ipilimumab trials and the OPTiM trial.

Health state utility values from NICE TA321 (Dabrafenib for treating unresectable or metastatic BRAF V600 mutation positive melanoma) were used in the model. Disutility values associated with AEs were obtained from a proprietary study commissioned by the company. Resource use and costs were estimated based on information collected in the company's resource utilisation study, published sources and the views of clinical experts.

The company has proposed a Patient Access Scheme (PAS). This is currently undergoing consideration by the Patient Access Scheme Liaison Unit and so only the results based on the list prices of T-VEC are presented in the CS.

For the comparison of T-VEC vs ipilimumab, implemented in the company model using the modified Korn model (or two-step Korn model), the company's incremental cost-

effectiveness ratio (ICER) per QALY gained was £1,458 (or £8,654). These figures were calculated using the full list price for ipilimumab. However, a confidential PAS means that ipilimumab is available to the NHS at an undisclosed price which is less than the list price. The company calculated ICERs per QALY gained for a range of discounts. Their results showed that in the analyses that used the modified Korn model (or two-step Korn model) to model the efficacy of ipilimumab the ICER remained below a threshold of £30,000 per QALY gained when a discount of 55% (or 10%) or less was assumed.

The company carried out a range of deterministic sensitivity analyses. The results show that the most influential variables were the duration of treatment and the prices of the two drugs. A number of scenario analyses were carried out. The two that had the most influence (impact of increasing the ICER per QALY gained by more than £5,000) were varying T-VEC dosing and the assumptions concerning routine treatment for non-progressive disease. The results of the company's probabilistic sensitivity analysis (PSA), using the list price, show that compared with ipilimumab implemented in the model using the modified Korn model (or two-step Korn model), the probability of T-VEC being cost effective is 98.39% (or 80.02%) at a threshold of £20,000 per QALY gained and 99.7% (or 81.83%) at a threshold of £30,000 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence

Following NICE's recent recommendation for the use of pembrolizumab for the first- and second-line treatment of patients with metastatic melanoma, the ERG considers that clinicians' first choice systemic treatment will shift away from ipilimumab towards pembrolizumab for all eligible patients. Hence, for patients with non-visceral metastatic melanoma, ipilimumab will only be the first choice comparator to T-VEC in the first- and second-line setting for a limited time period.

Due to a lack of either direct or indirect trial evidence that would allow a comparison between the efficacy of T-VEC and ipilimumab, the company developed evidence for the efficacy of treatment with ipilimumab using data from two clinical trials. The ERG has serious concerns relating to the reliability of this synthesised comparator:

1. Pooling ipilimumab data from the arms of two published clinical trials assumes that (a) dacarbazine and gp100 are both ineffective, (b) survival patterns are equivalent regardless of whether ipilimumab is administered as a first-line or as a subsequent line of therapy and (c) censoring occurs at a constant rate within each (arbitrary) time period. The ERG is not convinced that these assumptions can be substantiated
2. The modified Korn model was used to correct for differences in patient characteristics between two ipilimumab trials and the OPTiM trial. The main reason why the ERG considers that this model is not appropriate is that it was developed and calibrated

using data from patients with predominantly stage IV M1b and stage IV M1c disease, whilst it is patients with stage IV M1a disease who mostly feature in the OPTiM trial. Furthermore, in the OPTiM trial 54.7% of T-VEC patients had stage IIIB, stage IIIC or stage IV M1a disease compared with less than 20% in the ipilimumab trials

3. There is no information in the public domain relating to the way in which the original (published) Korn model has been modified or to the data used to calibrate the model. It is likely that the issues outlined in point 2 also hold for the modified Korn model. In addition, the modified Korn model includes an adjustment for elevated lactate dehydrogenase (LDH), which is not relevant for patients with stage IIIB, stage IIIC or stage IV M1a disease, but has the effect of reducing the size of the coefficients associated with other adjustment factors (and improving the relative efficacy of T-VEC)
4. The effectiveness of ipilimumab may vary significantly by stage of disease. The company has attempted to correct for this case-mix imbalance by using the two-step Korn model, which is a further application of the modified Korn model. This additional adjustment is likely to mean that the problems previously described are further compounded
5. The original Korn publication includes both PFS and OS models. The PFS model is quite different from the OS model. The ERG, therefore, concludes that the company's use of the same modified Korn model for both OS and PFS is inappropriate.

Within the company model, different methods are applied sequentially to estimate OS. A number of issues with this approach were identified by the ERG, including:

1. OS data from the earlier, less mature, data cut of the OPTiM trial were used by the company
2. The exponential trend used by the company to project OS for patients treated with T-VEC deviates markedly from the final recorded OPTiM trial data
3. For patients with stage I, stage II and stage III disease, the American Joint Committee on Cancer (AJCC) survival trends provide results from the date of diagnosis, whilst for patients with stage IV disease trends are recorded from the time of identification of first distant metastases. The relevance of these mixed AJCC adjusted mortality estimates is highly questionable
4. The data on which the AJCC analyses were performed were gathered prior to the current era of novel immunological treatments and may be unrealistic as these newer treatments have significantly altered the prospects for many patients
5. A sudden increase in the mortality rate after 270 weeks (62.1 months) is observed in the company model. The ERG considers that this effect is arbitrary and without any clinical justification
6. After 10 years, UK life table mortality rates are applied within the company model without adjustment, other than for age and sex. This implies that the cohort of long-term survivors is suddenly cured at this time point.

Other model-related issues identified by the ERG include an error in the discounting calculation, poor choice of health state utility values, lack of use of a terminal state disutility, use of a half-cycle (rather than a mid-cycle) continuity correction and a PSA ICER calculation error.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical evidence

- Results from the OPTiM trial show that the effectiveness of T-VEC is markedly improved in the subgroup of patients with stage IIIB to stage IV M1a disease when compared with the overall trial population (which includes patients with stage IV M1b and M1c disease)
- Evidence from the OPTiM trial suggests that the safety profile of T-VEC compares favourably to the safety profile of the comparators listed in the NICE scope
- The company has made thorough attempts to identify studies that include both a relevant treatment comparator to T-VEC and a relevant patient population.

Cost effectiveness evidence

- The company supported the appraisal process by providing the additional analyses requested by the ERG in a timely manner.

1.6.2 Weaknesses and areas of uncertainty

Clinical evidence

- Following the very recent approval of pembrolizumab for the first- and second-line treatment of patients with metastatic malignant melanoma, clinicians' first choice of systemic treatment for this population is likely to shift away from ipilimumab towards pembrolizumab
- The efficacy data for the anticipated T-VEC licensed population (patients with non-visceral metastatic melanoma) has been extracted from a post-hoc subgroup data analysis from the OPTiM trial
- The OPTiM trial may be subject to bias due to limited blinding and a higher proportion of dropouts in the GM-CSF arm (particularly in the first few months of the trial)
- The use of DRR as the primary endpoint in the OPTiM trial raises concerns as DRR is a new, albeit clinically relevant, endpoint which is non-validated and is potentially prone to bias
- The results of an FDA post-hoc analysis suggest that patients who had very small lesions (<1 cm^2) were more likely to respond to T-VEC than the overall population
- Two areas where evidence relating to treatment with T-VEC is lacking are in relation to line of treatment and long-term safety
- The relative clinical effectiveness of T-VEC compared with any treatment currently used in clinical practice is unknown.

Cost effectiveness evidence

- The ERG does not consider that the synthesised ipilimumab comparator is sufficiently reliable to support a valid assessment of the cost effectiveness of treatment with T-VEC vs ipilimumab
- The methods employed by the company to project OS for patients receiving T-VEC lack face-validity. Key issues are that the projection:

- Diverges from OPTiM trial data
- Shows a sudden increase in mortality at 270 weeks that is not supported by clinical evidence
- Includes an inappropriate use of AJCC data
- Is based on the assumption that all long-term survivors are cured at 10 years.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has formulated alternative methods to projecting survival for patients with non-visceral metastatic disease receiving T-VEC. However, due to the high degree of volatility exhibited in the model-generated results when the ERG amendments were implemented, and the serious problems identified relating to the construction of an ipilimumab comparator, the ERG does not consider that it is appropriate to present detailed alternative ICERs for this questionable comparison. However, it is possible to offer a broad indication of the relative significance of the issues identified:

- The company base case analysis uses the list price for ipilimumab and the proposed list price for T-VEC. Thus the current PAS price for ipilimumab is not applied. Results from the company model suggest that the estimated cost effectiveness of T-VEC is substantially worsened when a lower ipilimumab PAS price is implemented
- Taken separately, the ERG approach to estimating OS and PFS has contrary effects on estimated cost effectiveness: the revised OS estimate appears to improve the position of T-VEC, whereas the revised PFS estimate worsens it
- All of the other model-related issues identified are considered individually and all have a very small impact on the position of T-VEC, generally increasing the size of the estimated ICER when T-VEC is compared with ipilimumab
- When the PAS for ipilimumab is applied alongside the OS and PFS revised ERG estimates, the ICER per QALY gained is very severely increased far beyond the range normally considered acceptable by NICE
- The cost effectiveness of T-VEC compared to ipilimumab varies from dominating (more effective at less cost in the modified Korn model) to being dominated (less effective at greater cost in the two-step Korn model).

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

In Section 3.1 of the company's submission (CS), the company presents a brief overview of melanoma. In Section 3.2 of the CS, the company describes the effects of the disease on patients, carers and society. Information about the life expectancy of patients with the disease is presented in Section 3.4 of the CS. Key points from these sections of the CS are reproduced (as bulleted items) by the Evidence Review Group (ERG) in Box 1. While the ERG considers that these key points appropriately summarise the underlying health problems relating to melanoma in general, it is important to note that the evidence presented in the CS relates to a subgroup of patients with injectable disease, defined by disease staging.

Box 1 Summary of company's description of underlying health problem

Pathophysiology

- Melanoma is a malignancy of pigment-producing cells in the skin called melanocytes
- Superficial spreading melanoma, nodular melanoma, and lentigo maligna melanomas make up 90% of all diagnosed malignant melanomas
- Malignant melanoma is associated with high mortality due to the potential for: fast progression of disease; sudden relapse of disease; and a greater likelihood than other skin cancers to metastasise to distant hard to treat sites in the body
- If melanoma is detected before cancer cells have reached the blood vessels that are deeper in the skin, it can usually be completely removed with surgery. However, melanoma is often not detected in its earliest stages because the patient may not notice or bring attention to the lesion, or the clinician may not detect the melanoma at an examination
- The most common sites to which melanoma metastasises are lymph nodes, lung, liver, and brain, but it can metastasise to almost any organ and may affect many sites simultaneously

Incidence and survival

- Malignant melanoma is the fifth most common cancer in the UK with a total of 13,348 new cases diagnosed in 2011 (latest year available)
- The incidence of melanoma in the UK has risen sharply in recent years
- In the UK, malignant melanoma was responsible for 2,148 deaths in 2012 (latest year available)
- Survival rates for malignant melanoma vary dramatically according to the stage of the disease at diagnosis
- Although the treatment of malignant melanoma has progressed in recent years there is still a low 5-year survival rate of 20% to 34% for patients with stage IIIC disease and 5% to 22% for stage IV disease

Effects of disease on patients, carers and society

- Overall survival (OS) differs by stage of metastatic disease; however, even patients with non-visceral metastatic melanoma have a shorter median OS compared to patients with many other cancers
- Malignant melanoma … [is] one of the leading causes of lost life years due to cancer
- Melanoma can result in substantial impairment in health-related quality of life and psychological functioning
- Melanoma poses a substantial economic burden to society
- Lost productivity and travel costs incurred while receiving treatments further contribute to the societal burden of melanoma and can impact caregivers as well

Source: CS, Sections 3.1, 3.2 and 3.4

Disease staging

As stated in the CS, melanoma is considered advanced and described as metastatic disease if it has spread to surrounding lymph nodes (stage III) or to other parts of the body (stage IV). Malignant melanoma is classified in metastatic sub-stages, which encompass [either]:

1. Unresectable stage III disease with regional skin and/or lymph node involvement (M0)

   or

2. Distant metastatic disease (stage IV), to any site, with location either in:
   - skin (distant cutaneous or subcutaneous tissue) or distant lymph nodes (M1a)
   - lung (M1b)
   - any visceral organ and/or increased lactate dehydrogenase (LDH) levels in the serum, indicating aggressive tumour growth (stage IV M1c).

Non-visceral metastatic disease (T-VEC licensed population)

The evidence presented in the CS relates to a subgroup of patients with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC, and stage IV M1a) with no bone, brain, lung or other visceral disease. This is the expected T-VEC licensed population and the population for which the technology (talimogene laherparepvec [T-VEC]) is being appraised. Throughout the CS, and hereafter in this ERG report, this specific type of melanoma is referred to as non-visceral metastatic disease.

Patients with non-visceral metastatic disease make up a specific patient population that has rarely been studied in clinical trials. Hence there is little description of patients with this strictly defined disease type included in the CS. In the CS (page 29) it is stated that: “Overall survival (OS) differs by stage of metastatic disease” and, on page 36, that “…over 60% of patients with stage IIIB/C and stage IV M1a disease will eventually progress to visceral disease (stage IV M1b/c)”.[1-3]

Injectable melanoma

As T-VEC is administered only by intralesional injection, patients must have non-visceral metastatic disease as well as injectable melanoma. The company does not give any context regarding injectable disease in the CS. Injectable melanoma is however defined in the OPTiM trial[4] in the CS (Table 4-4) as:

- at least 1 injectable cutaneous, subcutaneous or nodal melanoma lesion ≥ 10mm in longest diameter or;
- multiple injectable melanoma lesions which in aggregate have a longest diameter of ≥ 10mm (draft European Public Assessment Report (EPAR),[5] page 64).

The ERG makes the following observations in relation to patients with injectable non-visceral metastatic melanoma:

- Patients who are considered to have injectable disease are typically those for whom lesions locally recur relatively frequently over several years and for whom there comes the point where simply surgically removing lesions becomes no longer a feasible treatment option due to the number of lesions and frequency at which they appear (e.g. 2 to 3 times a year) i.e. patients will eventually develop unresectable melanoma
- Such patients are typically those for whom it may be many years until their disease becomes visceral and hence have regionally or distantly metastatic (stage IIIB, stage IIIC, and stage IV M1a) disease with no bone, brain, lung or other visceral disease (metastatic non-visceral disease)
- The ERG considers that patients for whom T-VEC is most likely to be appropriate are those with stage III disease, i.e. patients with regional inoperable disease with small volume and little or no distant metastases
- Compared with patients who would not be considered to be eligible for injections, patients with exclusively injectable disease tend to have a better prognosis.

B-Raf proto-oncogene, serine/threonine kinase mutation positive or negative disease

In clinical practice, patients with metastatic melanoma are commonly tested for the presence of B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations since there are additional specific treatment options for patients who test BRAF mutation positive, namely BRAF inhibitors (see Section 2.2). It is estimated that 48% of patients with melanoma have BRAF mutation positive disease.[6] T-VEC is considered to be a suitable treatment option for patients with or without BRAF mutations since injectable tumours may be BRAF mutation positive or BRAF mutation negative.

2.2 Critique of company's overview of current service provision

Aims of treatment for patients with non-visceral and visceral metastatic disease

In Section 3.3 of the CS, the company presents an overview of current service provision for patients with metastatic melanoma and highlights the different aims of the therapies available to treat patients with non-visceral and visceral disease. While for both groups of patients the key aim is to improve long-term survival, for patients with non-visceral disease the primary goal of treatment is to maintain local and regional control and delay/prevent relapse or progression to visceral disease.[7] The company also states (CS, page 30) that "…OS is correlated with both level and durability of response/complete response to treatment. Importantly, complete response [CR] (i.e. the disappearance of all signs of cancer) significantly correlates with long-term survival in melanoma".[8,9]

Treatment options for patients with metastatic melanoma prior to 2011

The company observes that, historically, patients with metastatic disease have been treated with dacarbazine (DTIC) despite there being no clinically meaningful improvement in OS demonstrated by DTIC in randomised controlled trials (RCTs). British Association of Dermatologist guidelines for the management of cutaneous melanoma produced in 2010[10] recommended the use of DTIC as palliative chemotherapy. These guidelines also noted that although high-dose interleukin-2 has not been evaluated in a randomised Phase III trial, a small minority of patients may experience durable CRs; hence the guidelines[10] recommended that patients with stage IV melanoma should be considered for entry to clinical trials for treatment with interleukin-2.

Treatment options for patients with metastatic melanoma since 2011

Since 2011, a number of drugs have been licensed for the treatment of patients with metastatic malignant melanoma including ipilimumab, vemurafenib, dabrafenib, trametinib, nivolumab, pembrolizumab and cobimetinib (in combination with vemurafenib). However, only four of these agents are currently recommended by the National Institute for Health and Care Excellence (NICE): ipilimumab,[11,12] vemurafenib,[13] dabrafenib[14] and pembrolizumab.[15,16] Ipilimumab and pembrolizumab and are immunotherapies whereas vemurafenib and dabrafenib are BRAF inhibitors.

The company highlights that the NICE recommendations for treatment do not distinguish between sub-stages of metastatic melanoma. This is due in part to the design of the relevant clinical trials as they include a mix of patients in terms of disease stage. The company also states that the efficacy of the licensed treatments recommended by NICE is expected to be better in patients with non-visceral metastatic disease than in those with later stage disease;

however, the magnitude of the OS gain for patients with non-visceral metastatic disease is uncertain. Again, this uncertainty is due to the design of the relevant clinical trials.

To illustrate, in Table 1 the ERG has summarised data on patients and disease stage from five trials[17-22] of NICE recommended melanoma treatments alongside data from the OPTiM trial.[4] Fewer than 20% of patients had non-visceral metastatic melanoma in all five of the trials[17-22] of NICE recommended treatments compared with 57% of patients in the OPTiM trial.[4] Subgroup analyses have been conducted by stage of disease in all but one[21] of these trials. Importantly, the ERG notes that, with the exception of the OPTiM trial,[4] none of the subgroup analyses conducted included the group of patients who are the focus of this appraisal, namely patients with non-visceral malignant melanoma (stage IIIB to stage IV M1a disease).

The company notes that use of vemurafenib and dabrafenib is limited by the terms of their licences: patients must have BRAF mutation positive melanoma to be eligible for treatment with vemurafenib or dabrafenib. It is estimated that 48% of patients with melanoma have BRAF mutation positive disease.[6] Furthermore, clinical advice received by the company is that BRAF inhibitors are likely to be reserved for patients with more rapidly progressing disease and high disease burden. In clinical trials BRAF inhibitors have demonstrated relatively high overall response rates (ORRs) but these responses appear to be of limited duration, perhaps due to the development of treatment resistance.[23] In contrast, the company notes that ipilimumab has been shown to have a markedly more durable response. However, this marked benefit only exists for a small proportion of patients (whether BRAF mutation positive or wild type) who obtain a response.

Table 1 Proportion of patients by stage of disease and subgroup analyses conducted by stage of disease in trials of ipilimumab, vemurafenib, dabrafenib and pembrolizumab*

Trial and primary reference, N	Interventions (patient population)	Patients by disease stage (%)		Disease stage subgroups included in subgroup analyses
MDX010-20, Hodi et al 2010[19] N=676	Ipilimumab Ipilimumab + gp100 gp100 (Previously treated)	III IV M1a IV M1b IV M1c	1.5 9.2 17.9 71.4	III, IV M1a and IV M1b combined M1c
CA184-024, Robert et al 2011[22] N=502	Ipilimumab + DTIC DTIC (Previously untreated)	III IV M1a IV M1b IV M1c	2.8 15.9 25.1 56.2	III IV M1a IV M1b M1c
BRIM-3, Chapman et al 2011[17] N=675	Vemurafenib DTIC (Previously untreated)	IIIC IV M1a IV M1b IV M1c	4.9 11.0 18.8 65.3	IIIC IV M1a IV M1b M1c IIIC, IV M1a and IV M1b combined
BREAK-3, Hauschild et al 2012[18] N=250	Dabrafenib DTIC (Previously untreated)	III IV M1a IV M1b IV M1c	2.8 13.2 18.4 65.6	III, IV M1a and IV M1b combined M1c
KEYNOTE-002, Ribas et al 2015[20]* N=540	Pembrolizumab 2mg/kg Pembrolizumab 10mg/kg Chemotherapy of investigator's choice (Previously untreated)	III IV M1a IV M1b IV M1c	0.7 6.9 10.0 82.4	No subgroup analyses were conducted by disease stage
KEYNOTE-006, Robert et al 2015[21] N=834	Pembrolizumab 2mg/kg Pembrolizumab 10mg/kg Ipilimumab (Previously untreated with ipilimumab)	III IV M1a IV M1b IV M1c IV unknown ‡	3.9 10.2 18.8 65.3 1.8	No subgroup analyses were conducted by disease stage
OPTiM trial, Andtbacka et al 2015[4] N=436	T-VEC GM-CSF (previously treated and untreated)	IIIB IIIC IV M1a IV M1b IV M1c Unknown	7.8 22.2 27.1 20.6 22.0 0.2	IIIB and IIIC combined IV M1a IV M1b IV M1c IIIB, IIIC and IV M1a combined

GM-CSF= granulocyte-macrophage colony-stimulating factor
*All trials were Phase III trials except KEYNOTE-002 which was a Phase II trial
‡Further classification of disease stage was not provided

Treatment pathway for patients with non-visceral metastatic disease prior to December 2015

In Figure 3-2 of the CS, the company presents T-VEC as a potential alternative in clinical practice to all of the agents recently recommended by NICE for metastatic melanoma and for any line of treatment. The company argues: "…immunomodulators, such as ipilimumab, are the likely treatment options for patients with non-visceral metastatic disease (IIIB-IV M1a), for which T-VEC is indicated" (CS, page 34).

Furthermore, the company also highlights that all of the current treatment options can "…result in significant toxicity, which complicates treatment and affects quality of life for many patients already struggling with metastatic melanoma" (CS, page 37). Hence the company also argues:

> Clinical expert opinion suggests that for those patients with non-visceral metastatic disease and limited systemic disease, who would benefit from treatment to prevent progression to visceral disease, physicians may choose to adopt a wait and watch policy, because of the range of treatment limiting and potentially fatal immune-related adverse events associated with ipilimumab and the lack of less toxic alternatives treatment options. Therefore for patients with non-visceral disease and limited systemic disease, there remains an unmet need for effective therapies that provide a high complete response that is durable, a long term survival benefit, combined with an improved safety profile. (CS, page 37)

The ERG considers that the 'wait and watch' policy described in the CS reflects relatively common practice for patients with very limited cutaneous or subcutaneous disease and for whom ongoing excisions are not feasible. These patients are likely to have stage III disease rather than stage IV M1a disease. For these patients, ipilimumab (and BRAF inhibitors) would be deemed less attractive than a 'wait and watch policy' due potential toxicity associated with the drug (ipilimumab or BRAF inhibitors).

The ERG concurs with the company that, prior to December 2015, ipilimumab was the treatment of choice for the majority of patients with metastatic melanoma who were not suitable for a 'wait and watch' treatment. In particular, the ERG considers that the majority of patients with stage IV M1a disease would have been considered for treatment with ipilimumab.

In addition, the ERG notes that there are alternative treatment choices for selected patients with non-visceral metastatic disease, including isolated limb perfusion or electrochemotherapy, both of which are standards in melanoma care delivered in the UK, may be considered as options for patients with non-visceral metastatic disease. Indeed, electrochemotherapy has been identified in NICE guidance (IPG446)[24] as an option for this patient group. However, it is noted that the evidence base is limited:[25] approximately 160 patients from two RCTs,[26,27] three non-randomised comparative studies[28-30] and three case series.[31-33] Expert advice to the ERG has also highlighted that there is a range of other intralesional therapeutics available to treat this patient population.

Expected treatment pathway for patients with non-visceral metastatic disease from December 2015 onwards

Since the company presented its submission to NICE, pembrolizumab, another immunotherapy, has been recommended as a treatment option for patients with metastatic melanoma who have[15] and who have not[16] been previously treated with ipilimumab. The ERG considers that many patients with metastatic melanoma who have not been previously treated with ipilimumab will now be considered for treatment with pembrolizumab. This is particularly true for patients with stage IV M1a disease.

The ERG also considers that the 'wait and watch policy' or a regional treatment such as isolated limb perfusion or a procedure such as electrochemotherapy remain potential treatment options, particularly for patients with stage III melanoma. Pembrolizumab is considered to be less toxic than ipilimumab (as it is associated with fewer Grade 3 to 5 adverse effects and serious adverse effects compared with ipilimumab[21]). Therefore as clinicians are now able to offer pembrolizumab as a first-line treatment option, there are fewer patients likely to be considered for 'wait and watch' policy, a regional treatment such as isolated limb perfusion or a procedure such as electrochemotherapy than was the case prior to December 2015.

There is a small group of patients with metastatic melanoma who would not be treated with immunotherapy. These include patients with autoimmune diseases such as rheumatoid arthritis and inflammatory diseases such as ulcerative colitis.

Anticipated numbers of patients eligible for treatment with T-VEC

Sections 3.4 and 6.2 of the CS present an overview of the anticipated numbers of patients expected to be eligible for treatment with T-VEC. The company considers that 1,424 patients have stage IIIB to stage IV M1a melanoma in 2015 (9% of all patients with melanoma) and T-VEC would be an eligible treatment option in England for around half of these, namely 728 patients. The ERG notes that the estimated proportions (and definitions) of patients with stage III and stage IV melanoma have varied in recently conducted appraisals for NICE;[11-16] from 10% (1,190)[11] to 20% (2,330)[14] with stage III or stage IV disease (and similar estimates for stage IIIc to stage IV M1c disease: 10% [1,137],[15,16] 20% [1,993][13] or 21% [2,240][12]). The ERG therefore considers that the numbers of eligible patients estimated in the CS appears to be a reasonable estimate.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

The decision problem described by the company in the CS is presented in Table 2. It relates to the final scope issued by NICE. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 2 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company's submission
Population	Adults with stage IIIB to stage IV melanoma	Adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (disease stage IIIB to stage IV M1a) described within this submission as non-visceral metastatic disease
Intervention	T-VEC	T-VEC
Comparator (s)	-Ipilimumab -Vemurafenib (for people with BRAF mutation positive disease) -Dabrafenib (for people with BRAF mutation positive disease)	Ipilimumab is considered to be the primary comparator in the submission since BRAF inhibitors (vemurafenib and dabrafenib) are often reserved for those patients with rapidly progressing disease and high disease burden
Outcomes	-Overall survival -Progression-free survival -Time to treatment failure -Response rate -Adverse effects of treatment -Health-related quality of life	- Overall survival -Progression-free survival* -Time to treatment failure* -Response rate (durable response rate and overall response rate) -Adverse effects of treatment -Health-related quality of life
Economic analysis	In accordance with the NICE Reference Case which stipulates: The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	Cost effectiveness of treatments is expressed in terms of incremental cost per quality adjusted life year A lifetime time horizon reflecting any differences in costs or outcomes between the technologies being compared has been modelled Costs are considered from an NHS and Personal Social Services perspective
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on volume of disease and distribution of disease	The CS only includes patients from the pivotal OPTiM trial[4] with stage IIIB to stage IV M1a disease
Other considerations	None	None

BRAF=B-Raf proto-oncogene, serine/threonine kinase; CS=company submission; QALY=quality adjusted life year
Source: CS, adapted from Table 1-1

3.1 Population

The population specified in the NICE scope is adults with stage IIIB to stage IV melanoma. T-VEC does not currently have a licence in Europe for patients with melanoma. However, a positive opinion for the granting of a marketing authorisation has been issued by the Committee for Medicinal Products for Human Use (CHMP)[5] and is awaiting approval by the European Commission (expected in [redacted]) for adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease. These patients with non-visceral metastatic melanoma are referenced in the company's description of the population in the decision problem. Therefore, the clinical evidence presented by the company is only applicable to a subgroup of the patients specified in the NICE scope.

Importantly, but not explicitly stated in either the NICE scope or company's decision problem or in the anticipated licence, as T-VEC is administered by intralesional injection, the patient population is further restricted to patient's whose melanoma is considered injectable, i.e. there must be cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance. Patient experience of injectable treatments is not discussed in the CS. The ERG is not confident that all patients with injectable melanoma will be accepting of this type of treatment every 2 weeks over a long period of time.

Just under three-quarters (73%) of patients with metastatic non-visceral disease are considered by the company to have injectable disease. The population in the OPTiM trial[4] is therefore not directly comparable with patients in other trials for two reasons: (i) as noted by the ERG in Section 2.2 (Table 1), no other trial has conducted a subgroup analysis of patients with stage IIIB to stage IV M1a disease and (ii) only the OPTiM trial[4] has included patients solely with injectable disease.

3.2 Intervention

The intervention specified in the CS and in the company's decision problem statement is an oncolytic virus, T-VEC, derived from the herpes simplex virus type-1 (HSV-1) that has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein granulocyte-macrophage colony-stimulating factor (GM-CSF). The aim of treatment is to boost the body's immune system to protect itself from carcinogenesis and progression of cancer.[34,35]

T-VEC has two complementary mechanisms of action in/on cancerous cells:[36] (i) replication that causes cell rupture/lysis and death (intracellular or direct effect) (ii) post-lysis release of

tumour-derived antigens and GM-CSF, stimulating a systemic immune response from antigen-presenting cells (APCs) upon distant tumour sites (extracellular or indirect effect). Since T-VEC is a live virus, it would be administered in key centres of excellence with established oncology units. Staff need to be given specific training to be able to administer T-VEC.

T-VEC is administered by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance. It is provided in single use 1mL vials. According to the draft Summary of Product Characteristics (SmPC),[36] and as administered in the pivotal OPTiM trial,[4] the total injection volume for each treatment visit should be up to a maximum of 4mL. The initial recommended dose is up to a maximum of 4mL of T-VEC at a concentration of 10^6 (1 million) PFU/mL. The second dose, which is administered 3 weeks later, and then all subsequent doses, which are administered every 2 weeks thereafter, should be administered up to a volume of 4mL at a concentration of 10^8 (100 million) PFU/mL. The volume of T-VEC to be injected into each lesion is dependent on the size of the lesion, as described in Table 2 of the draft SmPC.[36] It is highlighted within the draft SmPC[36] that patients may experience an increase in the size of existing lesion(s) or the appearance of a new lesion prior to achieving a response. Therefore, as long as there are injectable lesion(s) remaining, T-VEC should continue to be administered for a minimum of 6 months, unless the patient's treating physician considers that the patient is not benefitting from it or that other treatment is required. It is stated within the draft SmPC[36] that T-VEC may be reinitiated if new lesions appear following a CR, assuming the physician considers that the patient will benefit from treatment. A maximum duration of treatment is not specified in the draft SmPC.[36] In the OPTiM trial,[4] the maximum duration of treatment was 18 months.

3.3 Comparators

Comparators currently used in clinical practice

Although the comparators listed in the NICE scope are ipilimumab, vemurafenib and dabrafenib, clinical advice provided to the ERG suggests that currently, in clinical practice, for many patients the most appropriate comparator with T-VEC may be pembrolizumab, 'wait and watch', a regional treatment such as isolated limb perfusion or a procedure such as electrochemotherapy.

Comparators with T-VEC in clinical trials

There has, to date, only been one Phase III RCT of T-VEC (OPTiM trial[4]). In this trial, T-VEC was compared with GM-CSF, which was administered by subcutaneous injection for 14 days, followed by 14 days of no injections, in a 28-day cycle. The company describes GM-

CSF as a potentially immunologically active agent. Indeed, the Food and Drug Administration (FDA) notes that, when the OPTiM trial[4] was in its design stage, GM-CSF was being considered as a possible treatment for melanoma.[37] It was noted in a recent review of oncolytic viruses as therapeutic cancer vaccines[38] that GM-CSF mediates anti-tumour effects by recruiting natural killer cells and by induction of tumour antigen-specific cytotoxic T cells through the action of antigen presenting cells. However, as the company states, GM-CSF is not licensed as a treatment for cancer. Rather, the ERG notes, it is commonly used as a support medication to accelerate the recovery of white blood cells following chemotherapy. Used in this manner, GM-CSF requires fewer injections (at a higher dose) than were administered in the OPTiM trial.[4]

As highlighted in Section 2.2 of this report, at the time the OPTiM trial[4] was planned and conducted (recruitment took place between 29 April 2009 and 8 June 2011), approved treatment options for patients with metastatic melanoma were largely limited to DTIC and interleukin-2, which, as stated by the European Medicines Agency (EMA) in the European Public Assessment Report (EPAR),[5] are known to have limited clinical effectiveness. Since T-VEC contains the GM-CSF gene insert, it was thus considered that this arm would serve as an important control to investigate whether GM-CSF alone could be responsible for the efficacy observed from treatment with T-VEC.

Comparators in NICE scope and in company's decision problem

Ipilimumab and the BRAF inhibitors, vemurafenib and dabrafenib, are all relevant comparators specified in the NICE scope and referenced in the company's description of the decision problem. Importantly, and as noted in Section 2.2 of this report, none of these interventions have been studied solely in patients with non-visceral metastatic melanoma.

Primary comparator in the company's decision problem

The company states: "…the primary comparator for the licensed T-VEC population is considered to be ipilimumab, although all three comparators [ipilimumab, vemurafenib and dabrafenib] are evaluated within the submission (CS, page 48)." Ipilimumab is considered to be the primary comparator because, prior to December 2015, ipilimumab was the most commonly used treatment for patients with non-visceral metastatic disease. There are two main reasons for this: (i) ipilimumab is a treatment option for patients regardless of their BRAF mutation status, whereas patients must have BRAF mutation positive melanoma to receive a BRAF inhibitor (ii) patient response to ipilimumab is more durable than with BRAF inhibitors, albeit with a lower response rate, and so BRAF inhibitors are usually reserved for patients requiring a rapid response to disease progression (who would most likely, therefore,

have more advanced disease than those with non-visceral metastatic disease). The ERG concurs with the company.

Since neither T-VEC nor GM-CSF have been directly compared to any of the comparators specified in the NICE scope, the company considered carrying out an indirect treatment comparison. However, the OPTiM trial[4] is an isolated trial in that it cannot be linked to published trials evaluating the comparators listed in the decision problem as it does not share a common comparator with any of these trials. It was not, therefore, possible to perform an indirect treatment comparison, and the company had to consider alternative methods for providing indirect estimates of the effectiveness of T-VEC comparators.

Consequently, both the modified Korn model and two-step Korn model were employed by the company to compare T-VEC with ipilimumab (see Section 4.3.3 and Section 5.5.1) in the patients with non-visceral metastatic disease. Hence evidence was only presented in the CS for T-VEC vs GM-CSF (clinical effectiveness) and for T-VEC vs ipilimumab (clinical and cost effectiveness evidence).

The ERG notes that in the OPTiM trial,[4] T-VEC was administered both as a first-line and as a subsequent line of treatment. However, Section 4.4 of the draft SmPC[36] includes the warning that "Efficacy data for Imlygic [T-VEC] in the current second or later line treatment settings are limited."

ERG opinions relating to treatment options

The ERG considers that clinicians may use T-VEC as both a first-line and a subsequent line of treatment if the disease is still largely small volume with little or no distant metastasis.

The ERG considers pembrolizumab to be the first choice when considering treatment options for previously untreated (and treated, if eligible) patients. Pembrolizumab was not, however, specified in the NICE scope. This may be because NICE recommended the use of pembrolizumab in patients with non-visceral metastatic melanoma after the NICE scope for the current appraisal had been finalised.

The ERG considers that the results of a comparison of T-VEC with ipilimumab are clinically meaningful but only for a limited period of time. Until recently, ipilimumab was the treatment of choice for the majority of patients with non-visceral metastatic disease; however, there is now likely to be a shift towards using pembrolizumab instead of ipilimumab as the first choice treatment option in the first- and second-line setting.

3.4 Outcomes

The company states that clinical evidence is reported in the CS for all five outcomes specified in the scope: OS, progression-free survival (PFS), tumour response rate, adverse events (AEs) of treatment and health-related quality of life (HRQoL). In addition, time to treatment failure (TTF) was also reported instead of PFS for the OPTiM trial since patients could continue to receive treatment despite showing evidence of disease progression.[4] The definitions of these endpoints are presented in Section 4.2.2.

With regard to the reporting of tumour response rates, the ERG notes that these are commonly reported as ORRs, a measure of patients who are considered to be either CRs or partial responders (PRs) to treatment. These findings are often accompanied by findings reporting time to response (response onset) and duration of response. All of these outcomes are reported in the CS for the OPTiM trial.[4] However, durable response rate (DRR) was the primary outcome for the OPTiM trial[4] and is also reported in the CS. It is noted in the draft EPAR[5] that this is a new clinically relevant endpoint. However, it is also noted that DRR is a non-validated endpoint and is potentially prone to bias.

The ERG notes that, in the company model when referring to the OPTiM trial,[4] TTF is used as a proxy for PFS. In the draft EPAR,[5] a separate post-hoc analysis of PFS that differs to TTF is provided. Post-hoc analysis refers to those in which the hypotheses being tested are not specified before any examination of the data. This post-hoc analysis is based on a definition of PFS that is more commonly used in other trials of cancer therapies, namely the time from randomisation until first progressive disease per investigator assessment or death, whichever was earlier. TTF on the other hand is defined as the time from baseline until the first clinically relevant disease progression (PDr) (i.e. progressive disease associated with a reduction in performance status [PS]) where there is no response achieved after the PDr. Given it was possible for patients to be treated beyond progression in the OPTiM trial,[4] the ERG considers TTF is an appropriate endpoint in this trial. The ERG does however draw attention to the fact that TTF is not defined in the same way as PFS in the pivotal trials of ipilimumab,[19,22] in these trials the intervention drug was not permitted after progression.[19,22]

3.5 Economic analysis

As specified in the NICE scope, the cost effectiveness of treatments was expressed in terms of the incremental cost per QALY gained. Outcomes were assessed over a 30-year time horizon (equivalent to a lifetime) and costs were considered from an NHS perspective.

3.6 Subgroups

The company states that no subgroup analyses were considered in its decision problem and that none were specified in the NICE scope. The ERG notes that the majority of evidence in the CS only includes patients from the pivotal OPTiM trial with stage IIIB to stage IV M1a disease.

3.7 Other considerations

The company highlights that T-VEC has been recognised by the EMA (in the draft EPAR[5]) as a novel, first-in-class oncolytic immunotherapy treatment. [redacted] All currently NICE recommended treatments that are considered to be comparators to T-VEC in the NICE scope and company's decision problem are also subject to PAS agreements.[11-14]

No equity or End-Of-Life issues were identified by the company.

4 CLINICAL EFFECTIVENESS

4.1 Critique of systematic review methods and synthesis

4.1.1 Systematic review methods

A summary of the systematic review methods employed by the company with ERG comment is presented in Table 3. Overall, the ERG is satisfied that the review was comprehensive and that the eligibility criteria employed were consistent with NICE scope and with the company's decision problem.

Table 3 Summary and ERG comment on the systematic review methods used by the company

Review method	ERG comment
Searching	
• Company states that one broad search was carried out to identify RCTs and non-RCTs • Databases searched included Medline, Embase and CENTRAL • Grey literature was searched for clinical studies and conference abstracts	• Where available, appropriate search terms were used; however search strategy reported by the company in its appendices to the CS includes a search filter for RCTs • ERG was unable to replicate company searches since search terms were not available for all databases searched (or the grey literature searches) and the number of results derived from each search term were not reported
Eligibility criteria	
• Two independent assessors assessed study eligibility	• Use of two independent assessor improves quality of review
Data extraction	
• Two independent assessors extracted data • A pre-defined extraction form was used	• Comprehensive data extraction was undertaken
Quality assessment and risk of bias	
• Descriptive critical appraisal of all included RCTs and non-RCTs was undertaken using NICE recommended method	• Unclear if two independent assessors were employed • The same tool was used to quality assess RCTs and non-RCTs; use of a tool designed specifically to assess non-RCTs would have been more appropriate

CS=company submission; RCT=randomised controlled trial

4.1.2 Data synthesis strategy

A summary of the company's strategy for data synthesis is presented in Table 4. Overall, the ERG is satisfied that appropriate steps were attempted to present a comparison of T-VEC with a relevant comparator.

Table 4 Summary and ERG comment on data synthesis strategy employed by the company

Data synthesis strategy	ERG comment
Evidence synthesis: RCTs	
• Only one RCT was considered relevant to the decision problem (OPTiM trial[4]) and all aspects of this trial are reported in detail in the CS • Focus of the CS was on the subgroup of patients with non-visceral metastatic disease in OPTiM trial[4] (T-VEC licensed population) • It was not possible to carry out a meta-analysis due to lack of relevant studies of T-VEC	• Company presented comprehensive information relating to the OPTiM trial[4] in the CS • ERG considers it appropriate to focus reporting of OPTiM trial[4] results to T-VEC licensed population • ERG agrees that it was not possible to carry out a meta-analysis
• Since the OPTiM trial[4] did not include a relevant comparator, a "qualitative synthesis" of RCTs is also referred to in the CS • A summary of trial characteristics, trial methodology, population characteristics, outcome assessment and summary of risk of bias (but no results) of included trials are presented in the appendices to the CS	• The "qualitative synthesis" appears to amount to studies which were considered for inclusion in the systematic review once full papers of titles and abstracts were obtained but were then excluded • ERG notes it is unusual to extract and present so much information about such studies in a systematic review but this detail does show that the company has made thorough attempts to identify studies which include both a relevant comparator to T-VEC and a relevant patient population approximating the T-VEC licensed population
• To enable the efficacy of T-VEC to be compared with that of the comparators listed in the NICE scope the company attempted to undertake NMA of trials included in "qualitative synthesis" of RCTs • The company states "…all three comparators [i.e. ipilimumab, vemurafenib and dabrafenib] are evaluated within the submission" (CS, page 48) • Alternative approaches were investigated to enable an indirect comparison of T-VEC with ipilimumab	• Appropriately, a table describing the included RCTs for attempted NMA is presented in the CS as is a network diagram showing how the evidence is broken • No trial results are reported anywhere in the CS or appendices for vemurafenib or dabrafenib • Company adequately described the alternative approaches considered to enable an indirect comparison of T-VEC with ipilimumab; however some of the descriptions used in the Korn analyses were incomplete and more information became available to the ERG via the clarification process
Evidence synthesis: non-RCTs	
• A "qualitative synthesis" of non-RCT evidence is also referred to in the CS; Since only one non-RCT (Study 002/03;[39] NCT00289016) was considered relevant to the decision problem by the company, only information about this single non-RCT is presented in the CS	• Non-RCT evidence summary appropriately includes a summary of study characteristics, study methodology, population characteristics, outcome assessment, assessment of risk of bias and study results

CS=company submission; NMA=network meta-analysis; RCT=randomised controlled trial

4.2 Critique, analysis and interpretation of trials of the technology

4.2.1 Identified studies in the company's submission

In total, 59 studies (from 97 records) were included in the company's "qualitative synthesis" of RCTs. Only the OPTiM trial[4] included T-VEC as an intervention or comparator. Nine other studies[17-19,21,22,40-43] were included for consideration in a network meta-analysis (NMA); these were trials which included a comparison with ipilimumab, vemurafenib or dabrafenib, i.e. comparators relevant to the decision problem. All of the remaining 49 studies in the company's "qualitative synthesis" were considered to be irrelevant to the decision problem.

It was impossible to complete a network using the data available from the ten RCTs[4,17-19,21,22,40-43] and so a NMA could not be conducted. As noted in Section 3.3, ipilimumab is considered to be the primary comparator in the CS. The company considered a number of alternative approaches to compare T-VEC with ipilimumab indirectly. The company chose the modified Korn model and the two-step Korn model to enable a comparison to be made. These included data from the OPTiM trial[4] and two trials of ipilimumab: CA184-044[17] and MDX010-20.[19]

In total, 174 studies (from 178 records) and 13 ongoing studies were included in the company's "qualitative synthesis" of non-RCTs. Only one non-RCT (Study 002/03[39]) studied T-VEC monotherapy and was, therefore, considered by the company to be relevant to the decision problem. Like the OPTiM trial,[4] this study included patients with stage IIIC to stage IV M1c disease but, unlike OPTiM,[4] this study did not include any patients with stage IIIB disease. Results were not presented for patients with stage IIIC to stage IV M1a disease.

The ERG is satisfied that the company identified all potentially relevant studies (RCTs and non-RCTs) and is not aware of any additional studies that should have been included as part of the evidence base describing the clinical effectiveness of T-VEC.

4.2.2 Statistical approach adopted for the conduct and analysis of OPTiM trial

In this section, the ERG provides a description and critique of the statistical approach adopted to analyse data collected during the OPTiM trial.[4] Information relevant to the statistical approach taken by the company has been extracted from the clinical study reports (CSRs) for the primary analysis[44] and the final analysis,[45] the trial statistical analysis plan (TSAP),[46] the trial protocol[47] and the CS.

Trial population

All pre-specified primary, secondary and tertiary efficacy outcomes were analysed using the intention-to-treat (ITT) population, i.e. all patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received. The safety population included patients who received at least one dose of T-VEC or GM-CSF (per-protocol analysis). Both the ITT and safety populations included all patients enrolled into the OPTiM trial,[4] i.e. patients with stage IIIB to stage IV M1c disease.

Efficacy outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the OPTiM trial[4] are listed in Table 5.

The ERG is satisfied that all outcomes were pre-specified in the TSAP[46] and that all outcomes were fully reported in the relevant CSR (i.e. primary analysis[44] or final analysis[45]).

The ERG notes a number of issues in relation to the primary outcome (DRR):

- DRR is not a commonly used endpoint (neither primary nor secondary) in other trials of metastatic melanoma; in the draft EPAR[5] it is noted that this is a new clinically relevant endpoint. However, it is also noted that it is non-validated endpoint and is potentially prone to bias
- In an FDA briefing document,[37] the clinical meaningfulness of a response (and therefore DRR) is questioned for patients with already relatively small baseline lesions
- The definition of the primary endpoint allowed a patient to have a durable response (DR) even if the patient developed new lesions, relapsed, or progressed after the 6-month period when the DR was recorded.

Despite these issues, DRR is considered in the draft EPAR[5] to be an acceptable endpoint in this setting as it captures a relevant clinical effect of the treatment. The ERG's view concurs with that of the EMA.

Table 5 Analysis strategy for key efficacy endpoints in the OPTiM trial

Endpoint	Definition	Statistical method
Primary outcome		
DRR	Defined as the percentage of patients with CR or PR lasting ≥6 continuous months from the time the response was first observed and beginning within the first 12 months following treatment	Analysed using a two-sided unadjusted Fisher exact test
Secondary outcomes		
OS	The time from the date of randomisation to the date of death from any cause. Death was the event of interest. OS time was censored at the last date the patient was known to be alive when the confirmation of death was absent or unknown. Patients were censored at the date of randomisation if no additional follow-up data was obtained	Analysed using an unadjusted log-rank test. A Cox proportional hazard model was used to estimate the HR for treatment effect
Best overall response and tumour burden	Best overall response observed across all time points. Disease burden at a particular assessment time was defined as the sum of the products of the perpendicular diameters of all measurable tumours identified at baseline plus the sum of the products of the perpendicular diameters of all measurable new lesions that appeared since baseline	Lavin method (using actual tumour area measurements) was used; best tumour reduction was compared using a Wilcoxon Rank Sum test
Response onset	The time from the date of randomisation to the date of the first documented evidence of response. This may have extended beyond the planned study duration for however long the patient was followed. The achievement of response was the event of interest. If no response was observed, response onset was censored at the last tumour assessment date or at the time of the new anti-cancer therapy, whichever was earlier. In the event that there was one or more missed or partially missing assessments for response and the next assessment showed response, the patient should have been scored as response on the first date when complete information was available to declare response	Displayed using a K-M life-table and analysed with a log rank test
TTF	Calculated from baseline until the first clinically relevant disease progression (PDr) [i.e. progressive disease associated with a reduction in performance status)] where there is no response achieved after the PDr. PDr is the event of interest. The TTF was subject to censoring at the last tumour assessment if the patient had not yet experienced PDr. In the event that there was one missed or partially missing assessment for PDr and the next assessment showed PDr, the patient should have been scored as PDr on the visit showing PDr. If there was PDr following two or more missed assessments, the patient should have been censored at the time of the last tumour assessment before PDr	Displayed using a K-M lifetable and analysed with a log rank test
Duration of response	The longest individual period from entering response (PR or CR) to the first documented evidence of the patient no longer meeting the criteria for being in response or death, whichever was earlier. The duration of response was defined to be zero if no PR or CR was ever achieved. This allowed all responders and non-responders to be included in the calculations. If the patient was last reported to be either a PR or CR, the duration of response was subject to censoring at that point	Displayed using a K-M life-table and analysed with a log rank test
Response interval	Defined as the time from the date of randomisation to the date of the last documented evidence of response prior to any new anti-cancer therapy which may be given. Response interval was zero if no response was ever achieved. This allows all randomised patients to be included in the analysis but post onset of response was censored if the patient is still in response at the last observation, which may extend beyond the planned study duration for however long the patient is followed	Displayed using a K-M life-table and analysed with a log rank test

CR=complete response; DRR=durable response rate; HR=hazard ratio; K-M=Kaplan-Meier; OS=overall survival; PDr=clinically relevant disease progression; PR=partial response; TTF=time to treatment failure
Source: CS, adapted from Table 4-5

Outline of analyses

It was planned that the primary analysis of DRR would take place when no additional patients had the possibility of meeting the criteria for DR. An interim analysis of OS was planned after 250 events. The study duration for the OPTiM trial[4] was 12 months and patients who had successfully completed treatment were eligible to enter a 6-month extension study which aimed to assess the long-term safety and efficacy of T-VEC.

The planned assessment of outcomes is summarised in Table 6.

Table 6 Outcomes pre-specified to be assessed at each analysis

Data cut / analysis[a]	Data cut-off date	Efficacy outcomes assessed
Primary	21 December 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 HRQoL
Primary OS Pre-specified to occur after 290 events	31 March 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) Pre-specified to occur after all patients had been followed for at least 3 years after randomisation	8 August 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; HRQoL= health-related quality of life; ORR, objective response rate; OS=overall survival
Source: Response to the ERG's clarification letter, Table A-10

Cox proportional hazard modelling

The analyses carried out by the company to generate OS, time to first response onset and duration of response hazard ratios were conducted using Cox proportional hazards modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. The company does not mention carrying out any testing to identify whether the assumption of proportional hazards holds. The ERG considers that this lack of testing casts doubt on the reliability of the generated hazard ratios.

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the OPTiM trial[4] is provided in Table 7. Having carried out these checks the ERG is satisfied with the statistical approach employed by the company.

Table 7 ERG assessment of statistical approach used to analyse the OPTiM trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pages 58 to 59)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the final analysis CSR (Section 8.9)	The ERG notes that the changes detailed in the protocol amendments were unlikely to have been driven by the results of the trial and are therefore not a cause for concern. All protocol amendments were carried out prior to the analysis being conducted
Missing data approach	Provided in the CS (page 66)	In the case of missing or uninterpretable data, the company contacted the study investigator to try and resolve this data. Missing data were logged in case report forms. For the primary endpoint, the EAC was permitted to employ last value carry forward imputation to account for missing lesion assessments. The ERG is satisfied that the company took a suitable approach to handling missing data
Pre-specified subgroup analyses for the primary outcome	For DRR: • Line of therapy (first- vs second-line) • LDH (≤ULN vs >ULN) • Disease stage (stage IIIb/stage IIIc vs. stage IV M1a vs stage IV M1b vs stage IV M1c) • Sex (Male vs female) • Age (<50 vs ≥50) • HSV-1 status at baseline (negative vs positive vs unknown	The ERG is satisfied that all subgroup analyses were pre-specified in the TSAP and were fully reported in both the primary analysis and final analysis CSRs
Adverse events	Safety was assessed through summaries of all AEs, common treatment-emergent AEs, SAEs, AEs leading to discontinuation and fatal AEs	The ERG is satisfied that the results of all the AE data analyses are provided in both the primary analysis and final analysis CSRs
Health-related quality of life	Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM)	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=adverse event; CS=company submission; CSR=clinical study report; EAC=Endpoint Assessment Committee; ERG=evidence review group; HRQoL=health-related quality of life; HSV-1=herpes simplex virus type-1; LDH=lactate dehydrogenase; SAE=serious adverse event; ULN= upper limit of normal
Source: CS, CSRs and ERG comment

4.2.3 Characteristics of the OPTiM trial

The OPTiM trial[4] is a Phase III open-label RCT that enabled treatment with T-VEC to be compared with GM-CSF in patients with stage IIIB, stage IIIC, and stage IV melanoma that was considered to be injectable and not surgically resectable. The OPTiM trial[4] was conducted at 64 centres across Canada, South Africa, the UK and the United States of America. Patients were randomised in a 2:1 ratio to receive either T-VEC (n=295) or GM-CSF (n=141). Randomisation was stratified according to site of first recurrence, presence of liver metastases, disease stage and prior non-adjuvant systemic treatment. The primary endpoint of the OPTiM trial[4] was DRR. Secondary endpoints included OS, ORR, response onset, TTF, duration of response, risk of visceral and/or bone metastasis, evidence of local and systemic effects of T-VEC treatment, AEs and HRQoL.

Patients eligible for the OPTiM trial[4] were originally only those who had received one prior line of treatment. On 17 November 2009 (around 7 months after the first patient had been enrolled), a protocol amendment allowed patients who had received no previous treatment for metastatic melanoma to be enrolled.

All patients enrolled in the OPTiM trial[4] had stage IIIB to stage IV disease that was not surgically resectable, a common inclusion criteria for trials of melanoma treatments. A less common criteria of the OPTiM trial[4] was that patients were required to have lactate dehydrogenase (LDH) levels ≤1.5 x upper limit of normal. In addition, the disease had to be injectable. One of the specific criterion was "…multiple superficial melanoma lesions which in aggregate have a total diameter of ≥10mm." It was noted in the FDA briefing document[37] (page 20) that "…Inclusion of such subjects [with potentially very small lesions] raises concerns regarding the reliability of injection, and particularly reliability of measurement, both at the baseline and during assessments of response." The ERG concurs with the view of the FDA.

The volume of T-VEC to be injected into each lesion was dependent on the size of the lesion, as described in Table 2 of the draft SmPC.[36] This therefore involved much investigator discretion in terms of the selection of lesions to be injected, the number of lesions to be injected, the total dose administered, the dose administered into each lesion, and the frequency of injections.

4.2.4 Patient characteristics in the OPTiM trial

Of the 436 patients that comprise the OPTiM trial[4] ITT population, a total of 249 patients (57%) had non-visceral metastatic disease (stage IIIB to stage IV M1a), and this specific group is the focus of this appraisal. It is stated in the draft EPAR[5] that 33 (8%) of the ITT population were from the UK.

The ERG notes that despite the lack of randomisation within the subgroup, with the exception of Eastern Cooperative Oncology Group (ECOG) PS, the patient characteristics were well balanced for patients with non-visceral metastatic disease. The percentages of patients at each stage of disease for T-VEC vs GM-CSF were 13.5% vs 14% for stage IIIB disease, 40.5% vs 36% for stage IIIC disease and 46% vs 50% for stage IV M1a disease. However, for ECOG PS, 74% in the T-VEC arm and 63% in the GM-CSF arm had ECOG PS 0.

Furthermore, the company states that, overall, the baseline characteristics are similar across all patients with non-visceral metastatic disease. The ERG agrees with this assessment. The proportion of female participants was similar in the ITT population (41.4% and 45.4% in the T-VEC and GM-CSF arms, respectively) and in patients with non-visceral metastatic disease (43.6% and 45.3% in the T-VEC and GM-CSF arms, respectively). Mean age was also similar in the ITT population (63.1 and 62.9 in T-VEC and GM-CSF arms, respectively) and in patients with non-visceral metastatic disease (64.5 and 62.5 years in T-VEC and GM-CSF arms, respectively).

In the ITT population, 53.4% of patients in the OPTiM trial[4] had received prior treatment for metastatic melanoma (the proportion of pre-treated fstatuspatients with non-visceral metastatic disease was not reported). The type of treatment received in the trial differs from that which would be available for patients with metastatic melanoma in clinical practice today. It is therefore unclear if similar findings for pre-treated patients in the OPTiM trial[4] could be replicated in clinical practice in England.

Overall, despite differences in the types of previous treatments received, the ERG considers that the patient population in the OPTiM trial[4] is generally similar to the population that is likely to be considered for treatment with T-VEC in clinical practice in England.

4.2.5 Assessment of methodological quality and risk of bias of OPTiM trial

The company's assessments of risk of bias presented in the CS (Table 4-11) are reproduced, along with ERG comments, in Table 8. The ERG disagrees with the company's

assessment in relation to blinding and drop-outs and also highlights other issues not explored by the company's assessment, many of which were also identified by the EMA[5] and FDA.[37] In these reports, the EMA[5] and FDA[37] highlight issues which may have consequences for the results for the ITT population of the OPTiM trial.[4]

Table 8 Company's assessment of risk of bias for the OPTiM trial with ERG comments

Risk of bias criteria	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	No	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	Disagree, there was minimal blinding and some risk of bias from the manner in which response to treatment was evaluated
Were there any unexpected imbalances in dropouts between groups?	No	Disagree, a higher proportion of patients dropped out of the trial prior to receiving treatment in the GM-CSF arm than in the T-VEC arm
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree, but note that the evidence in the CS for the T-VEC licensed population is derived from a subgroup of the ITT population
Other	Not explored	Issues around DRR: • not a validated endpoint • subjectivity in terms of assessment • missing confirmatory scans for response and therefore DRR were reported to be the most common protocol deviation

DRR=durable response rate; ITT=intention to treat
Source: CS, adapted from Table 4-11

The ERG notes that the OPTiM trial[4] was an open-label trial. The lack of blinding in the OPTiM trial[4] is a concern. Perceived beliefs about the relative efficacy of T-VEC may have influenced decision making about whether to stop treatment (particularly in the GM-CSF arm) or be given another therapy. Furthermore, clinical assessments of response were subjective, susceptible to investigator bias, and could have ultimately influenced the determination of stable disease, CR, and PR. Not only could this have affected the secondary endpoint of ORR but also the determination of the primary endpoint, DRR. DRR is described by the EMA as "a new non-validated endpoint" (draft EPAR,[5] page 102) and therefore the EMA considered that potential sources of bias may have been introduced during the conduct or analyses of the data. The FDA briefing document[37] further notes that the predominance of patients with only very small baseline lesions raises concern regarding errors and inaccuracies in response assessment for lesions.

Although the OPTiM trial[4] was an open-label trial, data for the primary endpoint, DRR, were reviewed and confirmed by an independent, blinded Endpoint Assessment Committee (EAC). Central confirmation by the EAC of DR would normally be considered to act as a check against bias from a lack of blinding. The FDA briefing document[37] reported that in the ITT population, the investigators and EAC agreed on approximately 85% of assessments, whereas it is noted in the EMA report[5] that only one additional DR was identified by the EAC, this response occurred in the GM-CSF arm. However, the extent to which the blinded EAC minimises bias in the OPTiM trial[4] is debateable given that the EAC only evaluated information sent by investigators for patients with investigator-determined CR or PR, or those who reached 9 months on therapy (also highlighted by the EMA[5] and FDA[37]). As summarised in Table 9, not one patient in the GM-CSF arm had a PR or CR for 6 continuous months compared with 14.2% in the ITT population and [redacted] of patients with non-visceral metastatic disease in the T-VEC arm. Hence, it is noted in the FDA briefing document[37] that proportionately more patients in the GM-CSF arm (87%) than in the T-VEC arm (58%) were never evaluated by the EAC.

In addition, the company noted that TTF may be affected by the open-label nature of the trial as outcome assessors may have been influenced by knowledge of which treatment a patient had received when judging whether treatment failure had occurred. The ERG agrees, and therefore considers that TTF results should be interpreted with caution.

A concern, in many ways related to the lack of blinding, was the number of drop-outs in the GM-CSF arm (Table 11). Most notably, a higher proportion of patients in the GM-CSF arm withdrew from the study without ever receiving treatment [redacted] These patients were considered to be non-responders and so their withdrawal could have biased findings in favour of T-VEC. Having started treatment, the ERG also notes that those in the GM-CSF arm were also more likely to withdraw their consent, which is another potential source of bias and favours T-VEC. The FDA briefing document[37] reports that the proportion of ITT patients who discontinued treatment at 3 months was 56.0% in the GM-CSF arm compared with 29.2% in the T-VEC arm. This imbalance in drop-out rates could also have created bias in favour of T-VEC in terms of assessment of responses.

A summary of the reasons for discontinuing treatment and the reasons for discontinuing to participate in the trial is presented in Table 9.

Table 9 Summary of the reasons for discontinuing treatment and the reasons for discontinuing to participate in the OPTiM trial (primary analysis)

Reason for discontinuing treatment and from study	stage IIIB–stage IV M1a (T-VEC licensed population)		stage IIIB to stage IV M1c (ITT population)	
	T-VEC (n=163)	GM-CSF (n=86)	T-VEC (n=295)	GM-CSF (n=141)
Not treated (%)	[redacted]	[redacted]	**1.4**	**9.9**
Discontinued from treatment (%)	[redacted]	[redacted]	54.9	53.9
• Maximum allowed dose without PR/CR	[redacted]	[redacted]	8.8	6.4
• PR or CR for at least 6 continuous months	[redacted]	[redacted]	14.2	0
• Progressive disease	[redacted]	[redacted]	64.7	67.4
• Adverse event	[redacted]	[redacted]	3.7	2.1
• Deaths	[redacted]	[redacted]	1.7	2.1
• Consent withdrawn	[redacted]	[redacted]	3.4	8.5
• Physician decision	[redacted]	[redacted]	2.0	3.5
Discontinued from trial after receiving treatment (%)	[redacted]	[redacted]	96.9	70.2
• Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]
• Deaths	[redacted]	[redacted]	[redacted]	[redacted]
• Consent withdrawn	[redacted]	[redacted]	[redacted]	[redacted]
• Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
• Other	[redacted]	[redacted]	[redacted]	[redacted]

CR=complete response; PR=partial response
Source: CS, adapted from Figure 4-4 and Table 4-7, CSR (Primary Analysis), adapted from Table 14-1-1 and company's response to clarification letter, adapted from Table A-13 and Figure A-6

Importantly, the EMA has noted that early treatment discontinuation in the GM-CSF arm could have potentially disproportionately affected the OS results in favour of T-VEC.[5] However, the EMA also states that a sensitivity analysis submitted by the company clarified that the patients who discontinued early did not affect the observed treatment difference in the ITT population for OS (draft EPAR,[5] Table 32) or DRR (draft EPAR,[5] Table 37).

The EMA has also highlighted that there was a higher proportion of patients with major protocol deviations in the T-VEC arm (12.2%) than in the GM-CSF arm (3.5%).[5] Missing confirmatory scans were reported to be the most common protocol deviation (6.1% vs 0.7%, respectively). However the EMA states that an additional analysis of DR, imputing patients with major protocol deviations provided by the company had no major effect on the DRR findings.[5]

Despite the concerns raised by the EMA, it concludes: “In general, the study was well conducted and no major issues were raised as to the conduct or the validity of the data” (draft EPAR,[5] page 102). The FDA briefing document[37] appeared to be more cautionary in tone, particularly as it considered there was uncertainty about the clinical meaningfulness of DRR (unlike the EMA who was satisfied that the outcome was clinically meaningful) and given there was no clear OS benefit for T-VEC vs GM-CSF in the ITT population (see Section 4.2.6).

Overall, the ERG considers that there are a number of potentially important sources of bias in the OPTiM trial.[4] Nevertheless, these are not sufficient to question the validity of the findings in the subgroup of patients with metastatic non-visceral disease since it is unlikely that bias alone could explain the differences between arms (as reported in Section 4.2.6) in this subgroup.

4.2.6 Results from OPTiM trial

All pre-specified primary, secondary and tertiary efficacy outcomes from the OPTiM trial[4] have been reported by the company. The key results are summarised in Table 10. In both the ITT population and subgroup of patients with non-visceral disease, T-VEC is significantly more efficacious than GM-CSF for all key outcomes.

Table 10 Summary of key efficacy results in the OPTiM trial (final data cut)

Outcome	Patients with each type of AE (%)			
	Patients with non-visceral metastatic disease		ITT population	
	T-VEC (n=163)	GM-CSF (n=86)	T-VEC (n=295)	GM-CSF (n=141)
DRR by EAC assessment (%)	25.2	1.2	16.3	2.1
Unadjusted odds ratio (95% confidence interval)	28.6 (3.9 to 211.5)		8.9 (2.7 to 29.2)	
P-value	<0.0001		<0.0001	
ORR by EAC assessment (%)	40.5	2.3	26.4	5.7
P-value	<0.0001		<0.0001	
Median TTF by investigator assessment (months)	13.1	3.3	8.1	2.9
Hazard ratio (95% confidence interval)	0.28 (0.20 to 0.40)		0.43 (0.33 to 0.56)	
P-value	<0.0001		<0.0001	
Median OS (months)	46.8	21.5	23.3	18.9
Hazard ratio (95% confidence interval)	0.56 (0.40 to 0.79)		0.79 (0.62 to 1.00)	
P-value	0.0008		0.0494	

DRR=duration of response rate; ITT=intention to treat; OS=overall survival; TTF=time to treatment failure
Source: CS, adapted from Table 4-13, Table 4-16, Table 4-14 and clarification response, Table A-12 (patients with non-visceral metastatic disease) and appendices to CS, adapted from Table 1-13, Table 1-15, Table 1-17 and Table 1-14 (ITT population)

Subgroup analyses of ITT population

Subgroup analyses for DRR and OS suggested that the treatment effect of T-VEC may differ according to disease stage, prior non-surgical melanoma treatment, line of therapy, presence of visceral disease, and (for DRR only) by geographic region. The p-values for the tests for interaction for these subgroup analyses are provided in appendices to this ERG report (Section 11.1).

In an exploratory post-hoc analysis of data for patients in the ITT population which was presented in the FDA briefing document,[37] a larger proportion (30.4%) of patients with a DR had only very small lesions (<1cm^2) compared to the overall population (10.1%). The FDA interpreted this to suggest that patients who had larger lesions were less likely to respond to T-VEC, although it also cautioned that the clinical meaningfulness of a response (and therefore DRR) is questioned for patients with already relatively small baseline lesions.

Subgroup of patients with non-visceral metastatic disease

In the subgroup of patients with non-visceral metastatic disease, it was noticeable that the CR rate was higher in the T-VEC arm than in the GM-CSF arm (16.6% vs 0.0%; p < 0.001; primary data cut). Furthermore, results of an analysis presented in the draft EPAR[5] show that in patients with non-visceral metastatic disease, patients receiving ≥ second-line T-VEC also had improved DRR (17% vs 2%) and objective response (28% vs 2%) relative to GM-CSF. However the p-values for the tests for interaction for these subgroup analyses were not provided.

After treatment failure, a greater proportion of patients in the GM-CSF arm received subsequent ipilimumab, vemurafenib, dabrafenib, trametinib or an anti-PD1 antibody (such as pembrolizumab) than patients in the T-VEC arm (50% and 41% respectively in T-VEC licensed population). Ipilimumab was the most common subsequent treatment (37% of patients in both arms). Vemurafenib and anti-PD1 antibodies (such as pembrolizumab) were both more commonly given to patients who failed treatment with GM-CSF than T-VEC: 15% vs 9% (vemurafenib) and 5% vs 1% (anti-PD1 antibodies) respectively.

The annual survival rates for patients in the T-VEC licensed population were consistently higher in the T-VEC treatment group compared with the GM-CSF arm. After 3 years, the survival rate for patients in the T-VEC treatment group was 54.9% compared with a survival rate of 34.6% for patients in the GM-CSF treatment group. Moreover, the survival rate in the T-VEC arm appeared to be stable over 4 and 5 years, and the difference in long-term survival rates at 4-years between T-VEC patients and GM-CSF patients was more than 20% (48.9% vs 27.5%).

Summary of findings and ERG comment

The company states that the results from patients with non-visceral metastatic disease are in line with the results from the ITT population. The ERG notes that the magnitude of difference between arms for all endpoints is much greater in patients with non-visceral metastatic disease than in the ITT population. Given the potential risks of bias identified in Section 4.2.5, the ERG cautions that it is difficult to argue that there is a demonstrable OS benefit for T-VEC over GM-CSF in the ITT population. On the other hand, in patients with non-visceral metastatic disease, there does seem to be a demonstrable benefit; the difference in efficacy endpoints between arms is large and is unlikely to be explained by methodological bias.

It is further noted that the findings for patients with non-visceral metastatic disease are however derived solely from an analysis of an exploratory post-hoc subgroup. Carrying out such analyses risks identifying subgroups in which superior drug efficacy occurs only by chance. However, the ERG's primary concern is that the subgroup comprises a mixture of

patients with stage III and patients with stage IV disease. This is an issue as the disease trajectory for patients with stage III disease is likely to differ from that of patients with stage IV disease.

4.2.7 OPTIM extension study

Patients who had successfully completed treatment in the 12-month OPTiM trial[4] (i.e. if they did not have disease progression during the OPTiM trial[4] or had a CR but developed new lesions within 6 months) were eligible to enter into a 6-month extension study to assess the long-term safety and efficacy of T-VEC. A total of 31 patients (28 treated with T-VEC and 3 treated with GM-CSF) of the 436 patients from the OPTiM trial[4] entered the extension study. It is not reported how many of these patients had non-visceral disease.

In this study, patients continued with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity. Patients who entered the extension trial were included in both the analysis for the primary and final data cut-off.

Median duration of treatment in the T-VEC and GM-CSF arms was 23.0 weeks (range, 0.1 to 78.9 weeks) and 10.0 weeks (range, 0.6 to 72.0 weeks), respectively. Median potential follow-up (time from random assignment to analysis) was 44.4 months (range, 32.4 to 58.7 months) at the primary analysis of OS. Including treatment received in the OPTiM trial,[4] median treatment duration was 88 weeks (range: 29 to 177 weeks) for patients in the T-VEC arm and 100 weeks for patients in the GM-CSF arm (range: 54 to 120 weeks).

Results from the extension study are not reported in the CS.

4.3 Company's methods for providing indirect estimates of effect

As there were no head-to-head RCTs comparing T-VEC with any of the comparators listed in the NICE scope, the company considered performing a NMA but found that this was not feasible. The company subsequently considered alternative methods to obtain indirect estimates of effect, eventually choosing to use two approaches, the modified Korn model and the two-step Korn model. Ipilimumab data were obtained from two RCTs[19,22] and were adjusted to enable comparison with T-VEC survival data from the OPTiM trial.[4] In this section, the ERG outlines the company's approach to obtaining indirect estimates of effect.

4.3.1 Network meta-analysis feasibility assessment

In order to assess whether it would be possible to perform a NMA, the company considered the results of the "qualitative synthesis". The company found that no trials (other than the OPTiM trial[4]) evaluated T-VEC, and no trials evaluated GM-CSF in comparison to any of the relevant comparators. Hence, the OPTiM trial[4] was found to be an isolated trial, in that it cannot be linked to published trials evaluating the comparators listed in the decision problem as it does not share a common comparator with any of these trials. Therefore, the company decided it was not possible to conduct a NMA. The ERG concurs with the company's view.

4.3.2 Network of evidence

Despite the isolated nature of the OPTiM trial,[4] the company decided to construct a broken network of Phase III trials in order to present and describe the network of evidence relevant to the decision problem. To identify the relevant evidence, the company examined the 59 studies identified in the "qualitative synthesis" and selected Phase III trials which were conducted in the population of interest (adults with stage IIIB to stage IV melanoma), which included at least one treatment arm receiving the intervention of interest or a relevant comparator (i.e. T-VEC, ipilimumab, vemurafenib or dabrafenib) as a monotherapy, and which reported data for either OS or PFS (TTF and not PFS data was utilised from the OPTiM trial[4]). Table 11 provides a summary of the ten studies that met these criteria and Figure 1 shows the resulting broken network.

Table 11 List of studies included in the network of evidence

# in Figure 1	Trial name and primary reference	Trial design	Trial drugs (n per arm)	Dabrafenib	GM-CSF	Ipilimumab	T-VEC	Vemurafenib
1	CA184-024 Robert et al 2011[22]	Phase III, DB RCT	Ipilimumab + DTIC (n=250) DTIC (n=252)	--	--	yes	--	--
2	BRIM-3 Chapman et al 2011[17]	Phase III, OL RCT	Vemurafenib (n=337) DTIC (n=338)	--	--	--	--	yes
3	Check-Mate 067 Larkin et al 2015[41]	Phase III, DB RCT	Nivolumab 3mg/kg (n=316) Nivolumab 1mg/kg + ipilimumab 3mg/kg (n=314) Ipilimumab 3mg/kg (n=315)	--	--	yes	--	--
4	MDX01020 Hodi et al et al 2010[19]	Phase III, DB RCT	Ipilimumab + gp100 (n=403) Ipilimumab (n=137) gp100 (n=136)	--	--	yes	--	--
5	KEYNOTE-006 Robert et al 2015[21]	Phase III, OL RCT	Pembrolizumab 10mg/kg (n=279) Pembrolizumab 3mg/kg (n=277) Ipilimumab 3mg/kg (n=278)	--	--	yes	--	--
6	COMBI-V Robert et al 2015[43]	Phase III, OL RCT	Dabrafenib + trametinib (n=352) Vemurafenib (n=241)	--	--	--	--	yes
7	COMBI-D Long et al 2014[42]	Phase III, DB RCT	Dabrafenib + trametinib (n=211) Dabrafenib (n=212)	yes	--	--	--	--
8	BREAK-3 Hauschild et al 2012[18]	Phase III, OL RCT	Dabrafenib (n=187) DTIC (n=63)	yes	--	--	--	--
9	coBRIM Larkin et al 2014[40]	Phase III, DB RCT	Vemurafenib + cobimetinib (n=248) Vemurafenib (n=247)	--	--	--	--	yes
10	OPTiM trial Andtbacka et al 2014[4]*	Phase III OL RCT	T-VEC (n=295) GM-CSF (n=141)		yes		yes	

DB=double blind; DTIC=dacarbazine; OL=open label; RCT=randomised controlled trial
*The company cites the primary reference for the OPTiM trial to be a 2014 conference abstract by Kaufman et al[48]
Source: CS, adapted from Table 4-21

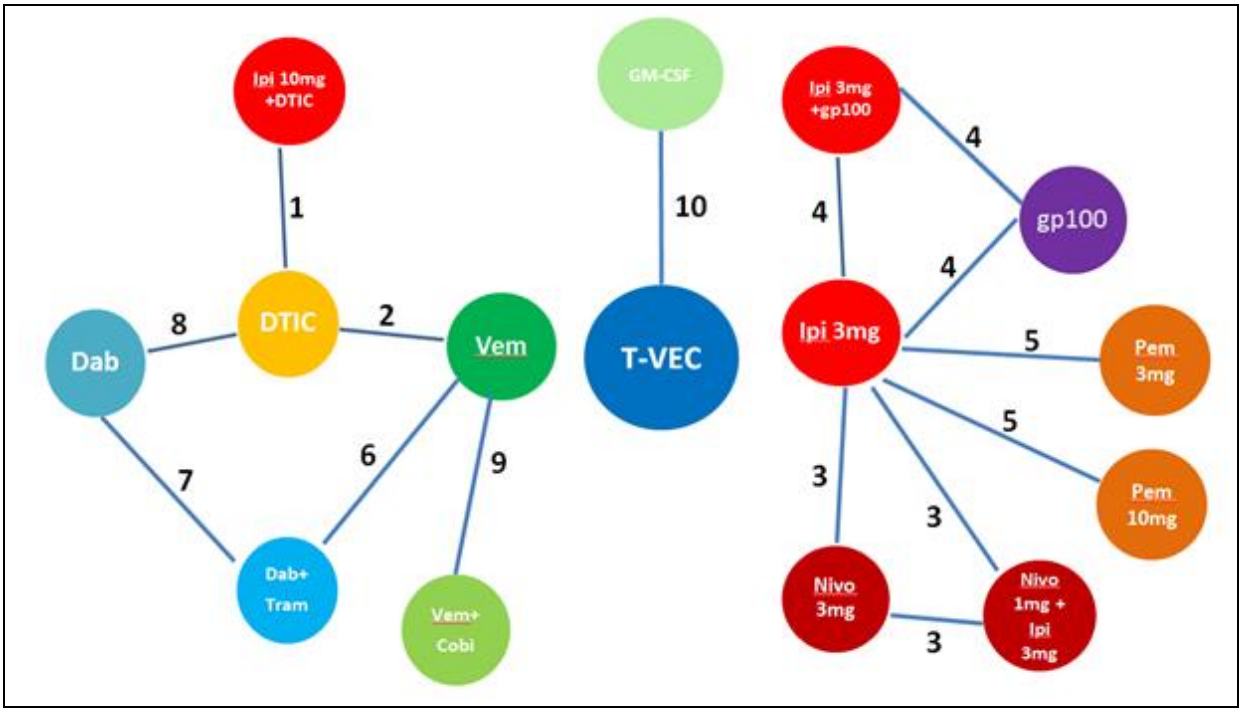


Figure 1 Network of evidence relevant to the decision problem
Note: Numbers correspond to # in Table 11 of this ERG report
Cobi=cobimetinib; dab=dabrafenib; DTIC=dacarbazine; GM-CSF=granulocyte macrophage colony-stimulating factor; gp100=glycoproteind100; nivo=nivolumab; ipi=ipilimumab; pem=pembrolizumab; tram=trametinib
Source: CS, Figure 4-11

The proportion of patients in the non-visceral metastatic disease subgroup varied widely between trials, ranging from 57% in the OPTiM trial,[4] to much lower percentages in the relevant comparator arms of the trials: ipilimumab (11%[19] to 17%[22]), vemurafenib (18%[17] to 23%[40]), and dabrafenib (16%[42] to 20%[18]). Most patients treated with ipilimumab, vemurafenib and dabrafenib had later stage metastatic disease (stage IV M1b to stage IV M1c). The company states that, as stage of disease is a known treatment effect modifier, the substantial differences between the proportions of patients at each stage within the trials introduce heterogeneity into the network, and therefore the RCTs are not comparable, even if a connected network were formed. The ERG concurs with this assessment.

The ERG further notes that the proportion of patients with injectable melanoma in these studies is unknown. Therefore the characteristics of patients with non-visceral metastatic disease in these trials may differ from those in the OPTiM trial.[4]

4.3.3 Assessment of alternative methods for comparative effectiveness

The company considered alternatives to a NMA to allow survival data from the T-VEC arm of the OPTiM trial[4] to be compared with survival data from other relevant RCTs. The main challenge was that the patient populations differed greatly across the RCTs identified as part of the relevant (broken) network of evidence (see Section 4.3.2 of ERG report). The relevant evidence for T-VEC comes from patients with non-visceral metastatic disease in the OPTiM

trial.[4] However, in the trials which evaluated the comparator treatments, results for this particular subgroup of patients were never reported; some reports did include subgroup analyses of patients by stage of disease, however, these groups did not categorise patients as having non-visceral metastatic disease defined as stage IIIB to stage IV M1a disease.

Since individual patient data were only available from the OPTiM trial,[4] only methods that attempted to adjust reported trial-level data for the comparator trials could be considered. The company considered six such methods for comparative effectiveness; a summary of the methodology and the company's evaluation of each method are provided in Table 12.

As the relevant data for T-VEC are derived from patients with non-visceral metastatic disease in the OPTiM trial[4] and the data available from the comparator trials are derived from whole trial populations which include patients with more advanced disease, it was necessary to account for differences in prognostic factors for OS and PFS (or TTF) between these populations. However, it was also important to consider whether there may be potential interactions between treatment and subgroups. The company claims that T-VEC is likely to have a greater treatment effect in patients with non-visceral metastatic melanoma than in the wider population of patients with all stages of metastatic disease. The ERG agrees that the OPTiM trial[4] evidence does appear to support this claim and agrees that this observation could be taken into consideration when choosing the most appropriate indirect comparison method. As shown in Table 12, the company rejected the matching-adjusted indirect comparison, simulated treatment comparison, and model-based meta-analysis methods as they fail to account for interactions between treatment and subgroups. Instead, the modified Korn model was employed as it captures prognostic differences between the trial populations in the comparator trials and in the subgroup of patients with non-visceral metastatic disease in the OPTiM trial,[4] and also allows for the interaction between T-VEC and patients with non-visceral metastatic disease. Since the modified Korn model does not allow for an interaction between comparators and the subgroup of patients with non-visceral metastatic disease, the company developed the two-step Korn model, even though it was uncertain whether an interaction between the comparator treatment and this subgroup of patients existed.

Table 12 Summary of the alternative indirect comparison methods considered and the company's evaluation of these methods

Method	Summary	Company's evaluation
Matching-adjusted indirect comparison (MAIC)[49]	IPD from trials of treatment A are matched to summary baseline characteristics from trials of treatment B. Survival outcomes for treatment A are adjusted (using an approach similar to propensity score weighting) so that the survival data for treatment A reflects survival if treatment A had been given to treatment B's patient population	**Not suitable** Does not allow for interactions between treatment and population with metastatic non-visceral disease
Simulated treatment comparison (STC)[50]	Similar to MAIC (uses IPD data for treatment A, and summary data for treatment B). STC creates a predictive equation for the survival outcome using treatment A IPD, in order to obtain survival data for treatment A as if it had been given to the patient population for treatment B	**Not suitable** Does not allow for interactions between treatment and population with metastatic non-visceral disease
American Joint Committee on Cancer (AJCC) adjustment[1]	Published, long-term survival data by stage of melanoma from the AJCC used to adjust survival outcomes based on disease stage for each trial	**Not suitable** Only adjusts for disease stage and no other variables, so may results in very limited adjustment for comparators
Korn prediction model[51]	Predicts OS using pooled data from 42 trials of 2100 melanoma patients, making adjustments for gender, ECOG PS, presence of visceral metastases, and presence of brain metastases[51]. Can be used to adjust OS and PFS from comparator trials based on patient characteristics from the intervention trial, so adjusted OS/PFS represent expected survival if patients in the comparator trials had a similar distribution of patient characteristics to those in the intervention trial	**Suitable with modification** A viable alternative method, but less appropriate than the modified Korn model, which includes an important fifth prognostic factor, elevated LDH levels
	Model-based meta-analysis (MBMA) can be used to implement the Korn model. MBMA uses a multivariable hierarchical survival model developed using the Korn algorithm as a reference	**Not suitable** Does not allow for interactions between treatment and population with metastatic non-visceral disease
Modified Korn model	First developed by Bristol‑Myers Squibb for the NICE appraisal of ipilimumab for previously untreated metastatic malignant melanoma,[11] the modified Korn model includes the original Korn prognostic factors, with the addition of elevated LDH levels as the fifth prognostic factor. Elevated LDH levels have been found to be an important independent prognostic factor in patients with metastatic melanoma.[52]	**Suitable** Due to the presence of important treatment-subgroup interactions, and the inclusion of elevated LDH levels as an important prognostic factor, the modified Korn model was chosen to be a suitable approach
Two-step Korn prediction model	Developed by the company; includes an adjustment for the fact that the data entered for ipilimumab are for the whole trial populations, whereas for T-VEC the data are from the stage IIIB to stage IV M1a disease subgroup. The method assumes there is an interaction between the treatment effect of ipilimumab and the earlier stage disease subgroup.	**Suitable** More conservative than the modified Korn model as it assumes ipilimumab would be more effective in a population with metastatic non-visceral disease than in the overall patient populations of the ipilimumab trials

AJCC=American Joint Committee on Cancer; Bristol‑Myers Squibb=Bristol Myers Squibb; ECOG PS=Eastern Cooperative Oncology Group performance status; IPD=individual patient data; LDH=lactate dehydrogenase; MAIC=matching-adjusted indirect comparison; MBMA=model-based meta-analysis; OS=overall survival; PFS=progression-free survival; STC=simulated treatment comparison

The company did not attempt to employ the modified Korn model or the two-step Korn model to adjust the survival curves of patients receiving BRAF inhibitors. The reason given for this was that the trials included in the meta-analysis which forms the basis for the original Korn[51] model did not differentiate patients by BRAF status. The ERG concurs with the company.

The results of the two-step Korn model are more conservative than the results from implementing the modified Korn model as the two-step approach assumes that ipilimumab is more effective in patients with non-visceral metastatic melanoma than in the wider population of patients with metastatic melanoma (predominantly later stage disease). Hence, the latter is considered to generate "best case" findings and the former "worst case" findings. More information about the Korn models is presented in the appendices to this ERG report (Section 11.2).

In summary, the trial results for T-VEC are: median OS: 46.8 months; mean OS: 36.9 months; median TTF: 13.1 months; mean TTF not reached; TTF is considered by the company to be a proxy for PFS. For ipilimumab, the adjusted results, as presented in the company's response to the ERG's clarification letter, are:

- Modified Korn model results for ipilimumab:
    - median OS increases from 10.9 months to 21.3 months (95% prediction interval: 14.6 months to upper interval not reached)
    - mean OS increases from 19.5 to 29.2 months (95% prediction interval: 23.8 months to 34.6 months)
    - median PFS increases from 2.8 months to 5.3 months
    - mean PFS increases from 8.0 to 15.2 months.
- Two-step Korn model results for ipilimumab:
    - median OS increases from 10.9 months to median not reached (95% prediction interval: 27.0 months to upper interval not reached)
    - mean OS increases from 18.0 to 32.3 months (95% prediction interval: 28.1 months to 35.8 months)
    - median PFS increases from 2.8 months to 17.6 months
    - mean PFS increases from 7.4 to 18.6 months.

Given the lack of clinical effectiveness evidence available, the ERG considers that the company was correct to attempt to apply alternative approaches for the comparison of T-VEC with ipilimumab. However, for reasons described in Section 5.5.1, the ERG does not consider that the use of either of the Korn models was appropriate. Therefore, the ERG does not consider the findings reported by the company when utilising the modified Korn model or the two-step Korn model to be either reliable or robust.

4.4 Safety

AE data are available for patients treated with T-VEC; these data have been previously reported for the OPTiM trial overall safety population (patients with stage IIB to stage IV M1c disease) in the published paper[4] and in the draft EPAR.[5] In the CS, the company reports only AEs for patients with non-visceral metastatic disease. Data for both populations are summarised by the ERG in Table 13 and a summary of the specific types of AEs and serious AEs (SAEs) is presented in the appendices of the ERG report (Section 11.3, Table 50).

Table 13 Summary of safety profiles of T-VEC and GM-CSF in the OPTiM trial

Type of safety concern	Patients with each type of AE (%)			
	Patients with non-visceral metastatic disease		Overall safety population*	
	T-VEC (n=163)	GM-CSF (n=76)	T-VEC (n=292)	GM-CSF (n=127)
All cause and any Grade treatment emergent AE	99	93	99	95
All cause treatment emergent Grade 3 to 5 AEs	33	23	[redacted]†	[redacted]†
All cause and any Grade treatment emergent SAE	20	13	26	13
All cause treatment emergent Grade 3 to 5 SAEs	NR	NR	[redacted]†	[redacted]†
Treatment-related AEs	93	79	93	80
Treatment-related Grade 3 to 5 AEs	14	5	[redacted]†	[redacted]†
Treatment-related SAE	6	0	7	0
Treatment emergent AE leading to discontinuation	9	7	10	6
Fatal AEs on study	1	0	3	2

AE=adverse event; NR=not reported; SAE=serious adverse event
Source: CS, adapted from Table 4-32 and *draft EPAR,[5] Table 46 except † taken from CSR, Table 12-2

The ERG concurs with the company that treatment emergent AEs, SAEs and treatment-related AEs were higher in the T-VEC arm than in the GM-CSF arm. In patients with non-visceral metastatic disease, AEs leading to treatment discontinuation were reported to be similar between arms and there was only one fatal AE, in the T-VEC arm, but this was not related to treatment. The ERG notes that treatment discontinuation rates due to AEs were marginally higher in the T-VEC arm than in the GM-CSF arm in the overall safety population.

Adverse events of special interest (AEOSIs) have also been identified by the company, and feature in the risk management plan (RMP), agreed with the EMA,[5] as being important safety concerns. These AEOSIs were not fully reported in the CS. The ERG has summarised the AEOSI data in Table 14; these events include flu-like symptoms, injection site reactions and cellulitis. The draft EPAR[5] states that the majority (70% to 90%) of the flu-like symptoms were reported to resolve within 72 hours. These events were also reported more frequently within the period of the first six treatments, particularly in patients who were HSV-1 negative at baseline, due to the intratumoral injection route of administration of T-

VEC. None of the serious cellulitis events resulted in study treatment discontinuation but study treatment was delayed as a result of cellulitis for one subject.

Table 14 Subject incidence of adverse events of special interest in the overall safety population of the OPTiM trial

Type of AEOSI	Patients with each type of AE (%)			
	T-VEC (n=292)		GM-CSF (n=127)*	
	AEOSI	SAEOSI	AEOSI	SAEOSI
Immune mediated events (autoimmune disorders)	2	≤1	2	0
Cellulitis at the injection site	6	2	2	≤1
Flu-like symptoms	90	3	65	0
Herpes simplex virus infections	6	0	2	0
Hypersensitivity	18	0	20	0
Injection site reactions	42	0	50	0
Vitiligo	5	0	2	0
Impaired wound healing at the injection site	6	0	2	≤1
Other neoplastic events (malignant/unspecified tumours)	6	3	2	≤1
Plasmacytoma	≤1	≤1	0	0

AEOSI=adverse event of special interest; SAEOSI=serious adverse event of special interest
Source: draft EPAR,[5] adapted from Table 49

To enable a crude comparison of T-VEC with ipilimumab, vemurafenib and dabrafenib, rates of dose discontinuations and/or modifications identified with these other agents are reported in the CS (pages 108 to 109 and Table 4-38). Similar data, supplemented by data from the pivotal pembrolizumab and T-VEC trials,[4,21] are summarised by the ERG in Table 15. These data show that T-VEC compares favourably in terms of safety when compared to other recommended treatments for metastatic melanoma.

It is highlighted in the draft EPAR[5] that data on long-term exposure to T-VEC are currently limited. Hence, a registry study is ongoing to monitor the long-term safety of patients who have received T-VEC as part of the RMP agreed between the company and the EMA[5] and a final study report is expected in July 2023.

Since T-VEC is an oncolytic virus, it is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding. There is the potential for transmission of infection from patients to close contacts or carers. The conduct of a Phase II multicentre, single-arm trial to evaluate the biodistribution and shedding of T-VEC in patients with non-visceral metastatic disease is included in the RMP detailed in the draft EPAR.[5] The primary analysis CSR for this study is anticipated to be released in August 2016 and the final analysis CSR is anticipated to be available in February 2017.

Table 15 Adverse events reported during pivotal trials with ipilimumab, vemurafenib, dabrafenib, pembrolizumab and T-VEC

Trial/ treatment	Frequency of any treatment emergent and/or treatment-related AEs, dose discontinuations and/or modifications due to AEs (%)		Common AEs	
MDX010-20[19]/ Ipilimumab (Previously treated)	Grade 3 or 4 treatment-related AEs	23	AEs were mostly immune-related which may involve the gastrointestinal, liver, skin, nervous, endocrine, ocular, or other organ systems	
	Treatment-related AEs leading to discontinuation	10		
BRIM-3[17]/ Vemurafenib (First-line)	Grade 3 to 5 AEs	50	Most frequently occurring Grade 3 or 4 AEs (%):	
	SAEs	33	Cutaneous SCC	19
	AEs leading to treatment discontinuation	7	Increase in LFT	11
	AEs leading to dose modification/ interruption	38	Keratoacanthoma	10
			Rash	9
			Arthralgia	6
BREAK-3[18]/ DTIC (First-line)	Grade 3 to 5 AEs	42	Most frequently occurring Grade 3 to 5 AEs (%):	
	SAEs	23		
	Treatment-related SAEs	15	Back pain	4
	AEs leading to treatment discontinuation	3	Hyperglycaemia	3
	AEs leading to dose reduction	18	Pyrexia	3
	AEs leading to dose interruption	27	GGT increased	3
KEYNOTE-006[21]/ Pembrolizumab (First-line)	Grade 3 to 5 AEs	35	Most frequently occurring Grade 3 to 5 AEOSIs (%):	
	Grade 3 to 5 treatment-related AEs	12		
	SAEs	25	Colitis	3
	Treatment-related SAEs	9	Hepatitis	2
	Treatment-related AEs leading to discontinuation	9	Diarrhoea	1
KEYNOTE-006[21]/ Ipiliumumab (First-line)	Grade 3 to 5 AEs	37	Most frequently occurring Grade 3 to 5 AEOSIs (%):	
	Grade 3 to 5 treatment-related AEs	20		
	SAEs	30	Colitis	7
	Treatment-related SAEs	18	Diarrhoea	4
	Treatment-related AEs leading to discontinuation	9	Hypophysitis	2
OPTiM trial[4]*/ T-VEC (Previously treated and untreated)	Grade 3 to 5 AEs	33	Most frequently occurring Grade 3 to 5 AEs (%):	
	Grade 3 to 5 treatment-related AEs	14		
	SAEs	20	Fatigue	2
	Treatment-related SAEs	6	Injection-site pain	1
	Treatment-related AEs leading to discontinuation	9		

AE=adverse event; AEOSI=adverse event of special interest; CS=company submission; GGT= Gamma-glutamyl transferase; LFT=liver function tests; SCC=squamous-cell carcinoma

*T-VEC licensed population only

Source: CS, adapted from Table 4-38 and text of pages 198 to 109 with additional data reported for BRIM-3[17] and BREAK-3[18] taken from ERG report submitted during the dabrafenib STA[53] and from the company's submission (Merck) for pembrolizumab for previously untreated ipilimumab naïve patients[54]

4.5 Health-related quality of life

Health-related quality of life data were only reported from the OPTiM trial[4] using the Functional Assessment of Cancer Therapy - Biologic Response Modifier (FACT-BRM) questionnaire. This questionnaire has a total of 40 items that are posed under six subscales:

1. Physical well-being
2. Social/family well-being
3. Emotional well-being
4. Functional well-being
5. Additional concerns-physical
6. Additional concerns-mental

Analyses were conducted to evaluate patient-level improvement in each of the above subdomains, as well as in three individual items:

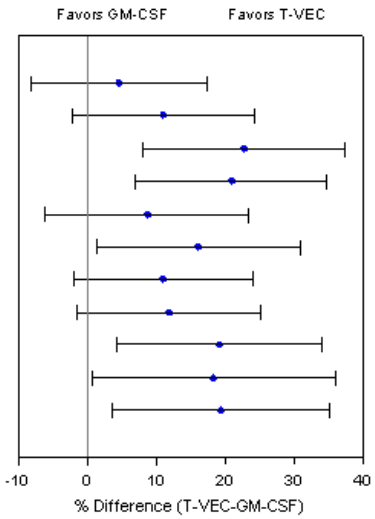
7. Overall quality of life [QoL]
8. Pain
9. Ability to work

In addition, the company describes:

10. Trial Outcome Index (TOI) score defined as the sum of subscales 1, 4, 5 and 6
11. Total BRM score (which appears to be the total score from all 40 questions).

The company reports that more patients treated with T-VEC than GM-CSF experienced improvements in HRQoL when they were assessed using these 11 measures. Between group differences reached statistical significance for six of the 11 measures: emotional well-being, functional well-being, social/family well-being, overall QoL, pain, and ability to work (CS, Figure 4-9). However, as recognised by the company, a substantial percentage of patients in the GM-CSF arm did not fully complete the questionnaires (CS, Table 4-19: by cycle 8 the response level from patients in the T-VEC arm was 56%, compared with 16% in GM-CSF arm) this is likely to be related to the differences between treatment arms in rates of treatment discontinuation, disease progression and death. The ERG therefore considers that HRQoL findings (reproduced in Figure 2) should be interpreted with caution.

Subscale	N	Rate GM-CSF	Rate T-VEC	% Difference (95% CI)
Trial Outcome Index	207	23.4%	28.0%	4.5% (-8.2% - 17.3%)
FACT-BRM Total	215	26.9%	37.8%	11.0% (-2.2% - 24.2%)
Emotional Well-Being	197	31.6%	54.3%	22.7% (8.1% - 37.3%)
Functional Well-Being	193	25.8%	46.6%	20.8% (6.9% - 34.6%)
Physical Well-Being	130	18.2%	26.7%	8.6% (-6.2% - 23.3%)
Social/Family Well-Being	152	21.6%	37.6%	16.1% (1.3% - 30.8%)
Additional Concerns: Physical	186	20.0%	31.0%	11.0% (-2.0% - 23.9%)
Additional Concerns: Mental	189	22.0%	33.8%	11.8% (-1.5% - 25.2%)
QoL	157	22.4%	41.7%	19.2% (4.3% - 34.1%)
Pain	106	20.6%	38.9%	18.3% (0.7% - 36.0%)
Ability to Work	134	20.0%	39.4%	19.4% (3.5% - 35.2%)



Scores from unscheduled visits were not included
A subject is considered evaluable for a domain if baseline score is not the best score and has at least one post-baseline score
TOI and total improvements are defined as >=5-point score increase from baseline with a >=1 cycle duration
QoL, pain and work improvements are defined as >=1-point score increase from baseline with a >=1 cycle duration
Other improvements are defined as >=2-point score increase from baseline with a >=1 cycle duration
Abbreviations: CI, confidence interval; GM-CSF, granulocyte–macrophage colony-stimulating factor; ITT, intent-to-treat; QoL, overall quality of life

Figure 2 Improvement Rates of Patient Report Outcome by Treatment of T-VEC and GM-CSF stage IIIB/C, stage IV M1a ITT Subjects Evaluable for Domain Improvement

Source: CS, Figure 4-9

4.6 Evidence from non-RCTs

Evidence from one Phase II non-RCT (Study 002/03[39]) is also presented in the CS. Unlike the OPTiM trial,[4] this study did not include patients with stage IIIB melanoma. In total, 23 patients had stage IIIC to stage IV M1a disease. Patient characteristics also differed to the characteristics of patients enrolled in OPTiM trial[4] in many other respects. The ERG therefore considers its findings are of limited relevance to the decision problem. The company, on the other hand, considers Study 002/03[39] provides supportive evidence of effectiveness. Information about this study, including study and participant characteristics and study results, is summarised by the ERG in the appendices (Section 11.4).

4.7 Conclusions of the clinical effectiveness section

The majority of evidence for the clinical effectiveness of T-VEC is derived from the OPTiM trial,[4] a relatively large (n=463), open-label, multi-centre, international Phase III trial which included patients from the UK (n=33 [8%]). ITT population (patients with stage IIIB to stage IV M1c disease) results show statistically significant improvements in favour of T-VEC vs GM-CSF for DRR, TTF (a proxy for PFS in this trial) and ORR but not for OS (although the OS gain was close to being statistically significant).

Findings from the OPTiM trial[4] were reported for patients with non-visceral metastatic melanoma (patients with stage IIIB to stage IV M1a disease); these patients are the focus of this appraisal as these are the patients for whom T-VEC will be licensed. Statistically significant improvements in DRR, TTF, ORR and OS were reported for patients treated with T-VEC compared with those treated with GM-CSF. The magnitude of the effect in the licensed population is much greater for all outcomes than in the ITT population. These findings were derived from an exploratory post-hoc analysis of 279 patients.

The ERG has concerns that the population considered in this STA comprises a mixture of patients with stage III and stage IV M1a disease as it is likely that the disease trajectory of patients with stage III disease differs from that of patients with stage IV disease. The ERG also considers that there are a number of potentially important sources of bias in the OPTiM trial[4] due to limited blinding, a higher proportion of drop-outs in the GM-CSF arm (particularly in the first few months of the trial), and the use of DRR as the primary endpoint. However, the ERG does not consider that the potential sources of bias explain the improvements in efficacy in the T-VEC arm compared with the GM-CSF arm reported for patients with non-visceral disease.

An area of uncertainty that has been raised by the FDA[37] relates to the size of lesions. The results of an FDA post-hoc analysis suggest that patients who had very small lesions (<1cm^2) were more likely to respond to T-VEC than the overall population (30.4% vs 10.1% respectively).[37]

In both the overall trial population and the subgroup of patients with non-visceral metastatic melanoma, there were more treatment emergent AEs, SAEs and treatment-related AEs in the T-VEC arm of the OPTiM trial[4] than in the GM-CSF arm. The types of AEs included flu-like symptoms (very common), injection site reactions (very common) and cellulitis (common and potentially serious). Careful wound care is important to minimise risk of infection, particularly if tissue necrosis results in open wounds. In terms of the types of AEs observed, T-VEC compares favourably in terms of safety to other recommended treatments

(pembrolizumab, ipilimumab, vemurafenib and dabrafenib) for metastatic melanoma. Although not reported in the OPTiM trial,[4] there is a potential risk for transmission of T-VEC and life-long latency with possible symptomatic herpetic infection due to reactivation. Long-term safety of T-VEC has not yet been established.

The ERG considers that the HRQoL findings from the OPTiM trial[4] should be interpreted with caution since a substantial percentage of patients in the GM-CSF arm did not fully complete the questionnaires. Furthermore, the findings comparing HRQoL for patients treated with T-VEC with those treated with GM-CSF are arguably of limited value since GM-CSF is not a relevant comparator in clinical practice. The same could be argued to be true for all findings of relative effectiveness for all other reported outcomes in the OPTiM trial.[4]

Pembrolizumab was not listed as a relevant comparator in either the NICE scope or the company's decision problem since both documents were produced when pembrolizumab was neither recommended by NICE nor used in clinical practice. However, the ERG considers that pembrolizumab is now likely to be the most appropriate comparator for patients with non-visceral metastatic melanoma in clinical practice.

Whilst, the ERG considers that a comparison with ipilimumab is clinically meaningful, it was not possible to conduct a NMA as the OPTiM trial[4] was found to be an isolated trial which could not be linked to any relevant published trials. Therefore, the company employed two alternative methods in an attempt to compare the efficacy of T-VEC with that of ipilimumab: the modified Korn model and the two-step Korn model. The ERG does not consider that either of the Korn models produces robust or reliable results. Hence, the relative clinical effectiveness of T-VEC vs ipilimumab is unknown. T-VEC does, however, appear to have a better safety profile than ipilimumab (and indeed, pembrolizumab).

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of T-VEC for treating patients with non-visceral metastatic melanoma. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's *de novo* economic evaluation. The company provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.2 The company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company undertook a search to identify studies reporting the cost effectiveness of T-VEC, compared with other therapies, for treating patients with non-visceral metastatic melanoma. Details of the search strategies employed by the company are included in Appendix 1.2 of the CS.

5.2.2 Eligibility criteria used in study selection

The application of the inclusion/exclusion criteria was a two-step process. First, the inclusion/exclusion criteria detailed in Table 16 were applied to the identified studies. The studies that were not rejected were then assessed for relevance. The company considered a study to be relevant if it included a comparator listed in the final NICE scope and had content that was applicable to the NICE reference case.

5.2.3 Included and excluded studies

The searches identified 10,667 titles. After the first eligibility assessment phase, 51 studies were considered to meet the inclusion criteria. However, only 11 (of the 51) studies met the relevance criteria. The identified studies comprised five NICE STAs,[11-15] four Scottish Medicines Consortium appraisals,[55-58] and two cost utility analyses.[59,60]

5.2.4 Findings from cost effectiveness review

Summary details relating to the 11 studies considered relevant are reported in the CS (Table 5-2).

5.2.5 Conclusions of the cost effectiveness review

None of the identified studies considered the cost effectiveness of T-VEC and therefore the findings from the review are of limited relevance to this STA.

Table 16 Economic evaluation search inclusion/exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of mixed cancer populations not reporting results for melanoma separately
Intervention/ Comparators	Not applicable	Not applicable
Outcomes	• Economic model methods • Incremental costs and QALYs • Other efficacy measures with associated costs • Incremental ICER outputs	Not applicable
Study Design	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses • Cost-consequence analyses	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	Not applicable
Date restrictions	Conference proceedings 2013 - present	Not applicable

HTA=health technology assessment; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; UK=United Kingdom
Source: CS, Table 5-1

5.2.6 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and stated inclusion/exclusion criteria and is confident that the company did not miss any relevant published papers.

5.3 ERG's summary of company's submitted economic evaluation

5.3.1 Model structure

The company has developed a de novo economic model to predict and compare the long-term costs and health outcomes associated with using T-VEC and ipilimumab to treat patients with non-visceral metastatic melanoma (stage IIIB to stage IV M1a disease). A schematic of the company's economic model is provided in the CS and is reproduced in Figure 3. It is a partitioned survival model comprising three mutually exclusive health states: non-progressive disease (comprising CR, PR and SD), progressive disease (PD) and death.

All patients enter the model in the non-progressive state and receive treatment with either T-VEC or ipilimumab. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state; that is, patients in the non-progressive state can move to either the progressive disease health state or to death, whilst patients in the progressive disease state can only move to death.

Estimates of OS for patients treated with T-VEC are based on survival data from the OPTiM trial.[4] Estimates of PFS for patients treated with T-VEC are based on TTF data from the OPTiM trial.[4] Estimates of OS and PFS for patients treated with ipilimumab have been generated using published data.[19,22,61-64] The proportion of patients in the post-progression state is calculated as the difference between OS and PFS at each time point.

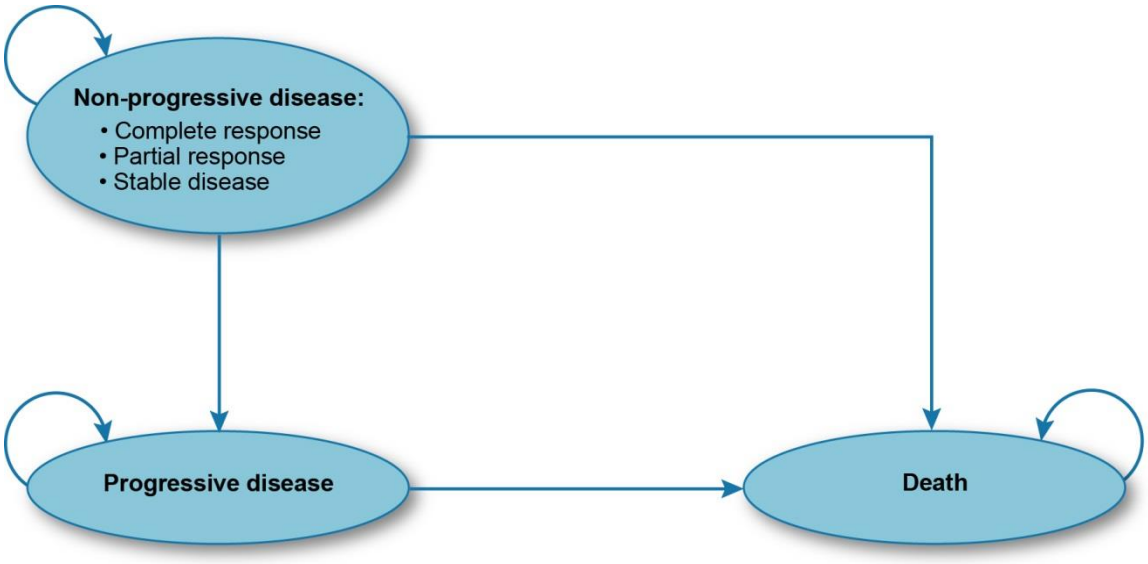


Figure 3 Schematic of company model

Source: CS, Figure 5-2

Patients receiving T-VEC were categorised into each health state based on the clinical definitions used in the OPTiM trial,[4] which are described in Table 17. The non-progressive

disease state is considered equivalent to PFS in the model, and TTF data are used as a proxy for PFS; thus the T-VEC non-progressive disease state is represented in the model by TTF data from the OPTiM trial.[4]

Table 17 Health state definitions used in the OPTiM trial

Health state		Definition	Reference
Non-progressive disease	CR	Disappearance of all clinical evidence of tumour	OPTiM[4]
	PR	≥50% reduction from baseline in the sum of the surface area of all measurable tumours	
	SD	Neither sufficient overall tumour shrinkage to qualify for response (CR or PR) nor sufficient tumour increase to qualify for PD	
Progressive disease	PD	>25% increase in the sum of the surface areas of all measurable tumours, or a single lesion increase of >25% (over the smallest measurement achieved for the single lesion), or the appearance of a new lesion	
Death		Death from any cause	-

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
Source: CS, Table 5-4

Patients in the ipilimumab arm are categorised into each health state based on the clinical definitions used in the pivotal clinical trials of ipilimumab (CA184-044[22] and MDX010-20[19]). Published PFS data from these trials[19,22] are assumed to be equivalent to the non-progressive disease state in the OPTiM trial.[4]

Upon disease progression, patients in both arms of the model are assumed to receive no further systemic treatment and, instead, receive best supportive care (BSC). BSC is defined in the CS as non-curative health care received by patients in the period between disease progression and administration of palliative care. Patients who die are assumed to have received palliative care for up to 3 months before death, and terminal care immediately prior to death.

The model includes five phases of disease management which are independent of active treatment. These are intended to address the differences in the quality of life, decrements in utility associated with AEs and the disease management costs associated with transitioning through the three health states:

- On-treatment pre-progression (routine treatment): the health care received while in the non-PD state
- On-treatment disease progression: the health care package received when switching to BSC because of disease progression
- BSC: the non-curative health care received in the period between disease progression and administration of palliative care
- Palliative care: the health care received up to 3 months before death
- Terminal care: the health care received immediately prior to death.

The model has been developed in Microsoft Excel and employs a cycle length of 1 week (with half-cycle correction). The time horizon is 30 years and health effects are measured in quality adjusted life years (QALYs). The perspective is that of the NHS and cost and outcomes are discounted at an annual rate of 3.5%.

Variants of the company model structure have been used previously in the modelling of advanced melanoma for previous STAs (Vemurafenib for treating locally advanced or metastatic BRAF mutation‑positive malignant melanoma [TA269],[13] Ipilimumab for previously untreated advanced [unresectable or metastatic] melanoma [TA319],[11] Dabrafenib for treating unresectable or metastatic BRAF mutation positive melanoma [TA321][14]).

5.3.2 Population

The population considered in the economic evaluation includes patients with unresectable regionally or distantly metastatic melanoma with no bone, brain, lung or other visceral disease (i.e. patients with stage IIIB to stage IV M1a disease) that may or may not have been previously treated.

The baseline patient characteristics used in the economic model are estimated using weighted averages from both arms (T-VEC and GM-CSF) of the OPTiM trial[4] and are presented in Table 18.

Table 18 Model population baseline patient characteristics

Characteristic	All lines: stage IIIB to stage IV M1a	PSA distribution	Source
Mean age, years	64	Fixed	OPTiM[4]
Proportion male, %	56	87.77 to 93.93 (gamma)	
Mean weight, kg	86	74.68 to 83.17 (gamma)	

PSA=Probabilistic sensitivity analysis
Source: CS, Table 5-3

5.3.3 Intervention and comparator

T-VEC

The recommended dosing schedule for T-VEC comprises an initial dose of up to 4mL at a concentration of 10^6 PFU/mL followed by subsequent doses of up to 4mL every 2 weeks at a concentration of 10^8 PFU/mL. Treatment with T-VEC is implemented in the model in line with the mean dose and treatment duration for the subgroup in OPTiM trial[4] who had stage IIIB to stage IV M1a disease. The mean dosage and treatment values do not include the accelerated dosing schedule allowed in the OPTiM trial protocol.[65]

Ipilimumab

The licensed dosing regimen for ipilimumab is 3mg/kg administered intravenously over a 90-minute period and given every 3 weeks for a total of four doses.[66] However, the company implemented ipilimumab treatment in the model in line with the mean dosage and treatment duration observed in the CA184-024[19] trial and reported in TA319,[11] which was slightly shorter than the currently recommended regimen and which the company states represents a conservative estimate which favours treatment with ipilimumab.

The mean dosage and treatment duration values used in the model are shown in Table 19.

Table 19 Mean dosing and treatment duration for patients receiving T-VEC and ipilimumab

Treatment	Dosage (including wastage)	Mean duration of treatment	Source
T-VEC	Cycle 1 (21 days): 2.86 vials of 10^6 pfu/mL Subsequent cycles (every 14 days): [redacted] vials of 10^8 pfu/mL	[redacted]	OPTiM[4]
Ipilimumab	52.20mL every 3 weeks (1.22 x 10mL vials and 1.00 x 40mL vial)	10.50 weeks (3.5 administrations)	Bristol-Myers Squibb[66] Hodi[19]

*All reported doses in the base case assume drug wastage
Source: CS, Table 5-18

Discontinuation rules

No clinical discontinuation rules were implemented.

5.3.4 Perspective, time horizon and discounting

The economic evaluation is undertaken from the perspective of the NHS. The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[67] both costs and outcomes are discounted at 3.5%.

5.3.5 Treatment effectiveness and extrapolation

Progression-free survival

The company states that the mode of action of T-VEC can lead to response happening post-progression, which renders inappropriate a standard definition of PFS. The company therefore use TTF data as a proxy for PFS. The TTF was defined as time from the first dose of study treatment until death or the 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 PS and/or that the patient requires alternative therapy in the opinion of the investigator.

In the company's base case, PFS for patients receiving T-VEC was modelled using a generalised gamma curve fitted to the OPTiM trial[4] TTF K-M data from week 0 to week 184 (at which point no more K-M TTF data were available). Hazards from the ipilimumab PFS arm were then applied to project PFS to 30 years.

The company base case for PFS associated with treatment with ipilimumab was based on published PFS K-M data from two trials.[19,22] The data from each trial were adjusted (to account for differences in the baseline characteristics between patients included in the T-VEC arm of the OPTiM trial[4] and patients included in the two ipilimumab trials[19,22]) using either the modified Korn model or the two-step Korn model. The modified data were then pooled and a generalised gamma curve was fitted to these data to project PFS to 30 years.

Overall survival

For patients treated with T-VEC, OPTiM trial[4] K-M OS data were used directly for the first 177 weeks. An exponential curve was then used to represent survival from week 178 to week 269 (at which point no further K-M data were available). From week 270 to 10 years, the company applied mortality rates calculated using combined data from the AJCC registry[1] and UK life tables.[68] UK life table mortality rates alone were applied from year 10 until 30 years.

OS for patients treated with ipilimumab was modelled using a similar multi-part extrapolation; however, cut points were implemented at different times to those used to model OS for patients treated with T-VEC. The OS projection for patients treated with ipilimumab was based on published K-M data from two trials,[19,22] which were adapted using either the modified Korn model or the two-step Korn model (to account for differences in the baseline characteristics between patients included in the T-VEC arm of the OPTiM trial[4] and patients included in the two ipilimumab trials[19,22]) and then pooled. These modified (and pooled) K-M data were used directly for the first 129 weeks, after which an exponential curve was used to represent survival until 239 weeks. Mortality rates calculated from AJCC registry data[1] and UK life tables[68] data were applied from week 240 to 10 years and then UK life table mortality rates alone were used until 30 years.

5.3.6 Health-related quality of life

The FACT-BRM questionnaire was used in the OPTiM trial[4] to assess patient HRQoL. However, the FACT-BRM is not a preference-based measure of HRQoL and does not conform to the NICE reference case. The company did not undertake mapping of the FACT-BRM. Instead, the company used utility values from NICE TA321[14] in the economic model. Utilities used in the base case are based on progression status, and patients with non-progressive disease are assumed to have the same HRQoL regardless of their response to treatment (CR, PR or SD). Within the model it is assumed that progression is a predictor of HRQoL and so patients with PD are assigned a lower utility value than those with non-progressive disease.

Table 20 Summary of utility values used in the company's base case

State	Mean utility value (standard error)	95% confidence interval	Source
Non-progressive disease (CR, PR, SD)	0.77 (0.011)	0.75 to 0.79	TA321[14]
PD	0.68 (0.084)	0.52 to 0.85	

CR=complete response; PD=progressive disease; PR=partial response, SD=stable disease
Source: CS, Table 5-12

The model also includes disutilities associated with grade ≥3 AEs (see Table 21). These values were obtained from a proprietary study commissioned by Amgen Limited.[69]

Table 21 Disutility values used in the company model

Adverse event	Mean utility value (standard error)	95% confidence interval	Source
Anaemia	0.09 (0.003)	0.083 to 0.097	Amgen[69]
Cellulitis	0.12 (0.005)	0.111 to 0.129	
Colitis	0.26 (0.010)	0.241 to 0.280	
Constipation	0.14 (0.005)	0.130 to 0.151	
Diarrhea	0.11 (0.004)	0.102 to 0.118	
Dyspnea	0.11 (0.004)	0.102 to 0.118	
Fatigue	0.05 (0.002)	0.046 to 0.054	
Headache	0.16 (0.006)	0.148 to 0.172	
Nausea	0.26 (0.010)	0.241 to 0.280	
Vomiting	0.26 (0.010)	0.241 to 0.280	

Source: CS, Table 5-12

5.3.7 Resources and costs

Drug costs

The anticipated list price for T-VEC at both the initial 10^6 PFU/mL and subsequent 10^8 PFU/mL concentrations is £1,445 per 1mL vial. [redacted]

The ipilimumab acquisition costs used in the model are based on the NHS list price, although the company acknowledges that a confidential PAS is available for ipilimumab in the NHS.

Drug acquisition costs and the mean acquisition costs per patient for both treatments are shown in Table 22.

Table 22 Treatment dosing schedule

Treatment	Vial volume (mL)	List price per vial[70]	Dosage (including wastage)	Mean duration of treatment	Mean cost per patient
T-VEC	10^6 PFU/mL x 1mL	£1,445*	Cycle 1 (21 days): 2.86 vials	[redacted][4]	[redacted]
	10^8 PFU/mL x 1mL	£1,445*	Subsequent cycles (every 14 days): [redacted] vials		
Ipilimumab	10mL (50mg)	£3,750	52.20 mL every 3 weeks (1.22 x 10mL vials and 1 x 40mL vial)	10.50 weeks (3.5 administrations)[19,66]	£68,038
	40mL (200mg)	£15,000			

*Anticipated list price
Source: CS, Tables 5-17 and 5-18 and company model

Administration costs

T-VEC is administered via intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. The company anticipates that administration of T-VEC will take place in a limited number of centres specialising in the treatment of skin cancers and that it will be administered in an outpatient setting in a designated side room (day case).

The company was unable to identify any Health Resource Group (HRG) codes specific to T-VEC, nor any other chemotherapy treatments administered in a similar fashion. It, therefore, assumed that the cost of administering T-VEC would be equivalent to that of ipilimumab (HRG code SB13Z).[71] The company states that this assumption is supported by its own

study[72] which was carried out to explore the administration cost of T-VEC. Further details of the Amgen Limited study are given in Appendix 1.8 of the CS.

Table 23 NHS reference costs

Description	Source	Unit price
Deliver more complex parenteral chemotherapy at first attendance- day case	NHS Reference Costs 2013/14[71] SB13Z	£316.95

NHS=National Health Service
Source: CS, Table 5-20

Health state unit costs and resource use

The company's systematic review of the economic literature identified only one study (the MELODY study[73,74]) that formally reported resource utilisation for melanoma in terms of inpatient, outpatient and hospice care requirements for a UK-specific cohort. The company notes that although the MELODY study[73,74] has been used in previous appraisals (TA319[11] and TA357[15]) it is of limited relevance as it was carried out some years ago, and predates current melanoma treatments and UK clinical practice. Instead the company carried out its own resource utilisation study[75] to collect costs throughout the treatment pathway for advanced melanoma. This study identified four treatment phases: active systemic treatment (pre-progression); disease progression; BSC/palliative care; and terminal care. Health resource utilisation (HRU) elements were identified for each phase, and estimates of the magnitude and frequency of their use in clinical practice were obtained through a UK Delphi panel, comprising seven oncologists. These costs were then applied in the model in five phases as BSC and palliative care costs were considered separately.

All data were obtained from NHS reference costs,[71] the Personal Social Services Research Unit (PSSRU),[76] and NICE TA268.[12] A one-off cost of £6,105 for terminal care was based on data published by the King's Fund.[77] All unit costs were inflated to 2013-2014 values using a PSSRU[76] published inflation index. A summary of the HRU estimates for each phase is shown in Table 24. Full details of the monthly HRU estimates for each phase are presented in Table 5-22 of the CS.

Table 24 Summary of resource use costs

Health state	Cost	Frequency
Non-progressive disease		
Routine treatment	£86.52	Per cycle
Progressive disease		
On progression	£1,198.50	One-off
Best supportive care	£91.24	Per cycle
Palliative care	£192.03	Per cycle
Terminal care	£6,105.00	One-off

Source: CS, Table 5-21

Adverse event costs and resource use

The company model includes Grade 3 or 4 AEs experienced by at least 2% of patients receiving any of the treatment options. These AEs were assumed to occur once and persist for 1 day. The costs were mainly derived from NICE TA319[11] and NICE TA269,[13] and were inflated to 2013/14 values. These costs are consistent with those reported in TA357 (Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab).[15] The values used in the model are summarised in Table 25.

Table 25 Adverse event costs applied in the model

AEs	Value	Source
Anaemia	£376.61	Cost assumed to be the same as for fatigue in NICE TA319
Cellulitis	£137.31	Cost assumed to be the same as for rash in NICE TA269 and inflated to 2014 cost
Colitis	£1,011.21	NICE TA319 inflated to 2014 costs
Constipation	£0	Cost assumed to be £0
Diarrhoea	£491.26	NICE TA319 inflated to 2014 costs
Dyspnoea	£0	NICE TA319; cost assumed to be £0
Fatigue	£200.79	NICE TA319 inflated to 2014 costs
Headache	£171.86	Cost assumed to be the same as for pain in NICE TA357
Nausea	£213.49	Cost assumed to be the same as for diarrhoea in NICE TA319
Vomiting	£213.49	Cost assumed to be the same as for diarrhoea in NICE TA319

Source: CS, Table 5-23

5.3.8 Cost effectiveness results

The company presents two sets of base case results for the comparison of T-VEC with ipilimumab. These differ in the approach used to project the efficacy of ipilimumab: the modified Korn model or the two-step Korn model. All results have been generated using list prices. Predicted (per patient) base case costs are presented in Table 26.

Table 26 Summary of predicted resource use by category of cost

Item	Treatment		Difference		
	T-VEC	Ipilimumab	Increment	Absolute Increment	% Absolute Increment
Modified Korn model					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.73%
Routine care costs	£17,083	£10,789	£6,294	£6,294	31.2%
On progression costs	£1,013	£1,080	-£67	£67	0.3%
BSC/palliative care costs	£12,885	£11,897	£989	£989	4.9%
Terminal care costs	£4,580	£4,986	-£406	£406	2.0%
Adverse events	£3	£118	–£115	£115	0.57%
Total	[redacted]	£98,219	[redacted]	[redacted]	[redacted]
Two-step Korn model					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.43%
Routine care costs	£18,198	£12,239	£5,959	£5,959	29.0%
On progression costs	£993	£997	-£4	£4	0.0%
BSC/palliative care costs	£10,647	£8,635	£2,013	£2,013	9.8%
Terminal care costs	£4,580	£4,696	-£116	£116	0.6%
Adverse events	£3	£118	–£115	£115	0.56%
Total	[redacted]	£96,035	[redacted]	[redacted]	[redacted]

Source: Company model

The incremental cost effectiveness ratios (ICERs) generated by the company model are presented in Table 27.

Table 27 Company base case cost effectiveness results using the modified Korn model and two-step Korn model to project survival for patients treated with ipilimumab

Treatment	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER per QALY gained
Modified Korn model							
Ipilimumab	£98,219	4.90	3.57	-	-	-	-
T-VEC	£100,166	6.66	4.91	£1,947	1.76	1.34	£1,458
Two-Step Korn model							
Ipilimumab	£96,035	6.16	4.61	-	-	-	-
T-VEC	£99,024	6.66	4.95	£2,989	0.50	0.35	£8,654

ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 5-25

When the modified Korn model is used to project the efficacy of ipilimumab the model results show that treatment with T-VEC leads to a lifetime increase in cost to the NHS of £1,947 per patient and delivers an additional 1.34 quality adjusted life years (QALYs) per patient. The resultant ICER for this comparison is £1,458 per QALY gained.

When the two-step Korn model is used to project the efficacy of ipilimumab the model results show that treatment with T-VEC leads to a lifetime increase in cost to the NHS of £2,989 per patient and delivers an additional 0.35 QALYs per patient. The resultant ICER for this comparison is £8,654 per QALY gained.

The company recognises that a confidential PAS (comprising a simple discount) means that the real cost of ipilimumab to the NHS is less than the list price. As the details of this PAS are not publicly available, the company calculated ICERs per QALY gained for a range of simple discounts (0% to100%) for ipilimumab. In the analyses that used the modified Korn model (or two-step Korn model) to model the efficacy of ipilimumab, the ICER remained below a threshold of £30,000 per QALY gained when a discount of 55% (or 10%) or less was assumed.

5.3.9 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a range of deterministic sensitivity analyses based around six variables: duration of treatment; response rates; administration costs; discount rates; health state utility values; and costs of terminal care. Variations in ICERs per QALY gained were generated by increasing and decreasing the parameter values by 20%. The ICERs per QALY gained for the ten most influential parameters following the modified Korn model and two-step Korn model are shown in Table 28 and Table 29 respectively.

Table 28 Ten most influential deterministic sensitivity analyses (modified Korn model)

Variable	ICER per QALY gained		Range
	20% decrease in base case value	20% increase in base case value	
Ipilimumab duration of treatment	£11,754	-£8,810	£20,564
Ipilimumab price	£11,647	-£8,732	£20,379
T-VEC duration of treatment	-£8,443	£11,359	£19,802
T-VEC price: main dose	-£6,850	£9,765	£16,615
T-VEC response rate: SD	£41	£2,874	£2,833
Ipilimumab response rate: PD	£2,385	£531	£1,854
T-VEC administration cost per cycle	£742	£2,174	£1,432
T-VEC price: first dose	£853	£2,063	£1,210
Discount rate: costs	£1,971	£986	£985
T-VEC response rate: PR	£1,015	£1,901	£887

ICER=incremental cost effectiveness ratio; PD=progressed disease; SD=stable disease; PR=partial response
Source: Company model

Table 29 Ten most influential deterministic sensitivity analyses (two-step Korn model)

Variable	ICER per QALY gained		Range
	20% decrease in base case value	20% increase in base case value	
Ipilimumab duration of treatment	£48,470	-£31,050	£79,520
Ipilimumab price	£48,056	-£30,747	£78,803
T-VEC duration of treatment	-£29,630	£46,939	£76,570
T-VEC price: main dose	-£23,469	£40,778	£64,247
T-VEC response rate: SD	£2,565	£14,744	£12,179
Ipilimumab response rate: SD	£11,513	£5,796	£5,717
T-VEC administration cost per cycle	£5,885	£11,424	£5,539
HSUV: PR	£6,827	£11,817	£4,990
Ipilimumab response rate: PD	£11,144	£6,165	£4,978
T-VEC price: first dose	£6,315	£10,994	£4,679

ICER=incremental cost effectiveness ratio; PD=progressed disease; SD=stable disease; PR=partial response; HSUV=health state utility value
Source: Company model

Scenario analyses

A wide range of scenario analyses was undertaken by the company to assess the structural and methodological assumptions implemented in the model. No scenarios had an impact greater than +/-£5,000 on the base case ICERs per QALY gained when using the modified Korn model. However, two scenarios had an impact of over £5,000 when using the two-step Korn model. These two scenarios were related to the inclusion of an accelerated dosing schedule for patients treated with T-VEC and to including zero costs for routine treatment for patients with CR. Results from these scenarios are shown in Table 30.

Table 30 Scenario analyses that change the ICER per QALY gained by at least £5,000

Parameter	Base case assumptions	Sensitivity analysis assumption	Modified Korn model		Two-Step Korn model	
			ICER per QALY gained	Difference from base case	ICER per QALY gained	Difference from base case
Base case result:			£1,458	-	£8,654	-
Varying the modelling approach for T-VEC dosing						
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: 2.86mL Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: 2.86mL Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	£4,124	+£2,666	£18,964	**+£10,310**
Varying resource use assumptions in routine treatment for non-progressive disease						
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and ipilimumab	Costs of routine treatment with CR assumed to be zero for both T-VEC and ipilimumab	£56	-£1,402	£2,958	**-£5,696**

CR=complete response; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, adapted from Table 5-32

Probabilistic sensitivity analyses

The company undertook two probabilistic sensitivity analyses (PSAs) to generate ICERs per QALY gained. One used the modified Korn model to model the efficacy of ipilimumab and the other used the two-step Korn model. The PSAs were carried out using 1,000 iterations of

the cost effectiveness model. The cost effectiveness planes for these comparisons are shown in Figure 4 and Figure 6 respectively, whilst the cost effectiveness acceptability curves (CEACs) are shown in Figure 5 and Figure 7 respectively.

When the modified Korn model was used to model the efficacy of treatment with ipilimumab the mean probabilistic ICER for T-VEC vs ipilimumab was £1,680 per QALY gained. This value is £222 greater than the deterministic ICER for this comparison. The CEAC shows that the chance of treatment with T-VEC being cost effective at a threshold of £20,000 (or £30,000) per QALY gained is 98.39% (or 99.7%).

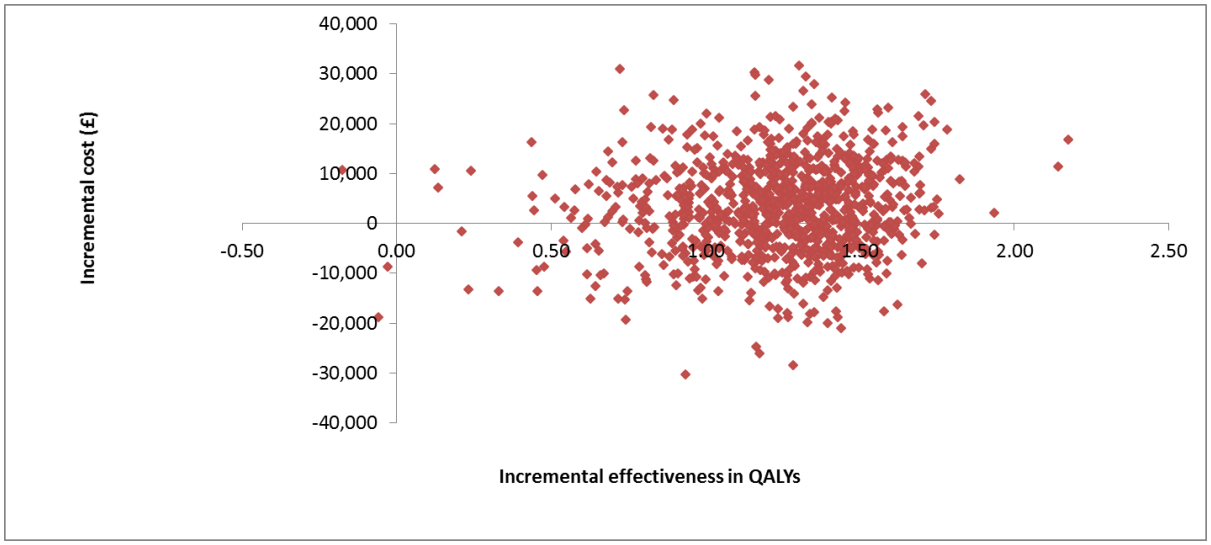


Figure 4 Cost effectiveness plane - modified Korn model
Source: Company model

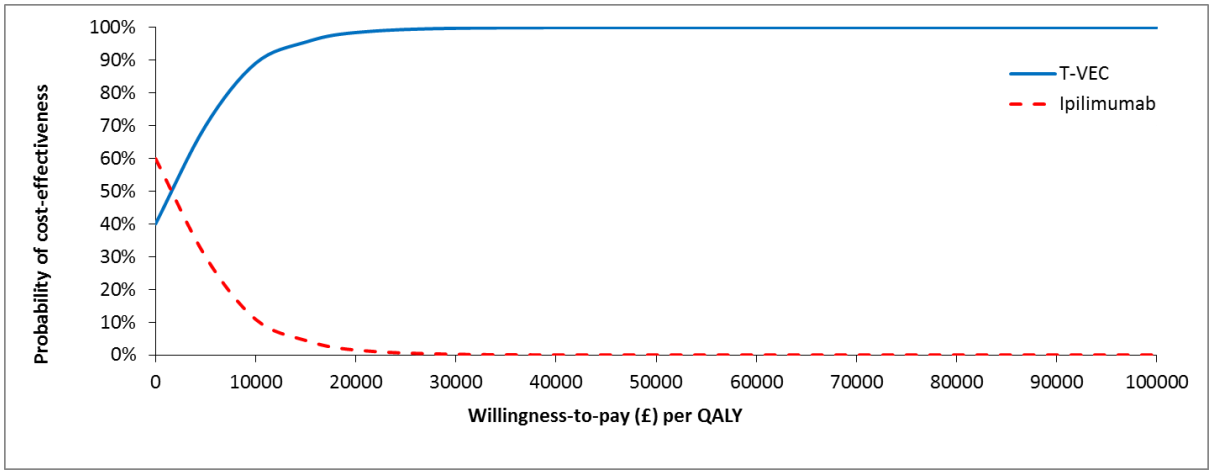


Figure 5 Cost effectiveness acceptability curve - modified Korn model (willingness-to-pay threshold £20,000)
Source: CS, Figure 5-42

When the two-step Korn model was used to model the efficacy of treatment with ipilimumab the mean probabilistic ICER for treatment with T-VEC vs ipilimumab was [redacted] per QALY gained, which is [redacted] less than the deterministic ICER. This reflects the inherent uncertainty in the calculation of the two-step Korn model. The CEAC shows that the chance of treatment with T-VEC being cost effective at a threshold of £20,000 (or £30,000) per QALY gained is 80.02% (or 81.83%).

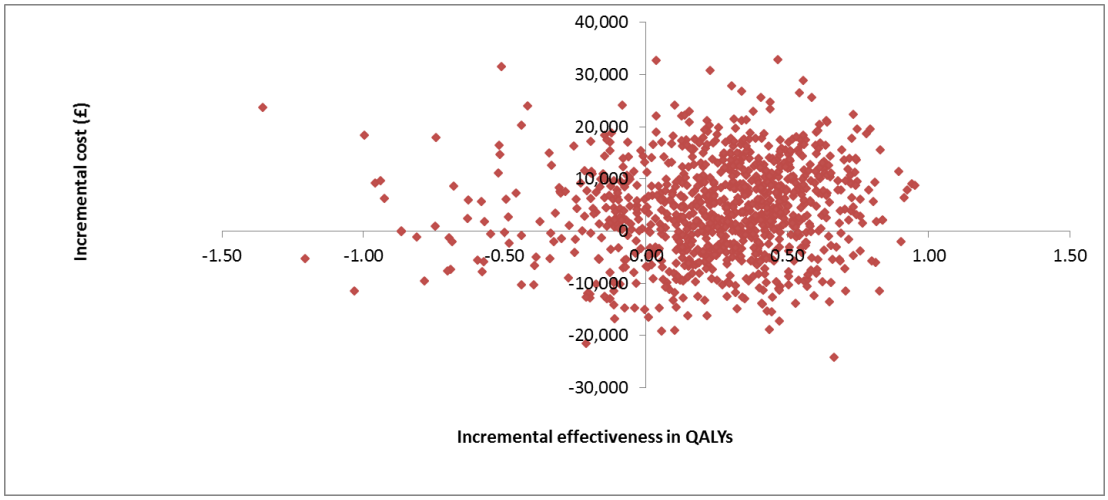


Figure 6 Cost effectiveness plane (two-step Korn model)
Source: Company model

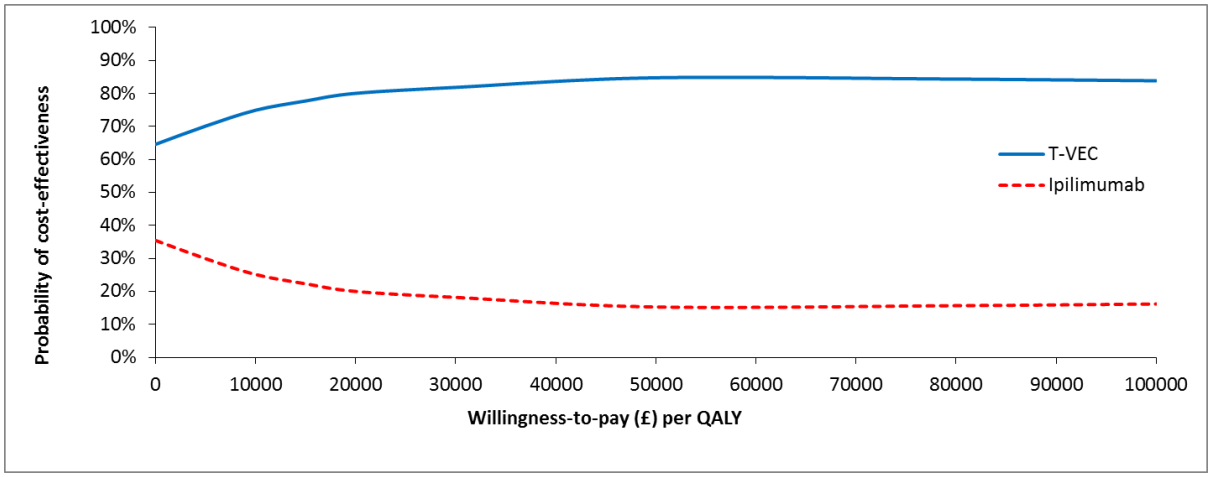


Figure 7 Cost effectiveness acceptability curve (two-step Korn model)

Source: CS, Figure 5-43

Table 31 and Table 32 show that the mean PSA and deterministic ICERs per QALY gained when the two different Korn models were used to model the efficacy of ipilimumab treatment. The PSA ICER generated when the modified Korn model was used is positive and similar to the associated deterministic ICER. However, when the two-step Korn model was used the mean PSA ICER is negative and substantially different from the deterministic ICER, which reflects the uncertainty in the estimate.

Table 31 Deterministic and PSA ICER results (modified Korn model)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
Deterministic results					
T-VEC	£100,166	4.91	£1,947	1.34	£1,458
Ipilimumab	£98,219	3.57			
Probabilistic sensitivity analysis results					
T-VEC	£101,212	4.79	£2,083	1.24	£1,680*
Ipilimumab	£99,129	3.56			

QALY=quality adjusted life years
*ERG calculated value from incremental cost and QALY values given in CS, as ICER given in CS was calculated incorrectly
Source: CS table 5-31 and company model

Table 32 Deterministic and PSA ICER results (two-step Korn model)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
Deterministic results					
T-VEC	£99,024	4.95	£2,989	0.35	£8,654
Ipilimumab	£96,035	4.61			
Probabilistic sensitivity analysis results					
T-VEC	£100,450	4.82	-£3,091	0.24	-£12,879*
Ipilimumab	£103,541	4.58			

QALY=quality adjusted life years
*ERG calculated value from incremental cost and QALY values given in CS, as ICER given in CS was calculated incorrectly
Source: CS table 5-31 and company model

5.3.10 Model validation and face validity check

Clinical benefit

The company compared the model's predicted outcomes for patients treated with T-VEC, both short- and long-term, with the reported outcomes from the OPTiM trial[4] and found them to be comparable. The company notes that the ipilimumab survival outputs estimated by the model (which are based on the modified Korn model and two-step Korn model) differ from clinical trial[19,22] results.

Model validation

The company states that the general model structure is consistent with metastatic melanoma models (TA321,[14] TA319,[11] TA269[13]) that have previously been accepted by NICE as part of STAs and that assumptions relating to current treatment options were supported by key opinion leaders practicing in the UK. The company reports that it used the input of these clinicians and health economic experts to inform the methods for survival analyses, dosing and application of AEs. The opinions provided by these experts were also used to inform the decision to use the modified Korn model and two-step Korn model to model survival for patients treated with ipilimumab.

The company reports that quality-control procedures for verification of input data and coding were performed by staff not involved in the model development. A checklist was used to verify the results, which were found to be consistent. Furthermore the input data were found to be robust to extreme values.

5.4 ERG's critique of the submitted economic evaluation

5.4.1 NICE reference case checklist

Table 33 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. The economic evaluation considers a subgroup of that issued in the final NICE scope in line with the anticipated licence. The decision problem addressed in the submission is adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (disease stage IIIB–stage IV M1a)
Comparator(s)	As listed in the scope developed by NICE	Partial. The company considers that BRAF inhibitors are unlikely to be treatment options for the stage IIIB to stage IV M1a population and that ipilimumab is the primary comparator
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	No – no connected evidence network is possible. A synthesised comparator was developed from three arms of two ipilimumab trials with adjustments to match baseline patient characteristics
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs, using utility estimates from other NICE appraisals which used the EQ-5D instrument
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes, HRQoL data were collected as part of the OPTiM trial[4] but these were not suitable for utility estimation
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes, partially - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model

EQ-5D=EuroQol-5 dimension; PPS=personal social services; QALY=quality adjusted life year

5.4.2 Drummond checklist

Table 34 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	No	The question was well-defined but could not be answered with the available trial data nor via standard methods of evidence synthesis
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	No direct RCT evidence or standard indirect evidence was available to compare the intervention to the selected comparator treatment
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Yes	-
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Sensitivity and scenario analyses were reported
Did the presentation and discussion of study results include all issues of concern to users?	Partially	Weaknesses in the methods used to synthesise a notional comparator were not fully explored

RCT=randomised controlled trial

5.5 Critique of cost effectiveness analyses

5.5.1 Reliability of the comparator used in the company model

The comparator employed in the company model as the basis for assessing the incremental cost utility of T-VEC is not the comparator employed in the OPTiM trial[4] (in this trial T-VEC was compared with GM-CSF). The comparator in the company model was synthesised from data describing the ipilimumab treatment arms of two clinical trials.[19,22] The reliability of this synthesised comparator depends upon six assumptions and are each considered in detail in this section:

a) Ipilimumab is the most appropriate comparator for T-VEC in the specified patient population (non-visceral metastatic melanoma)

NICE has very recently recommended pembrolizumab for both first-line and second-line[15] treatment of patients with metastatic malignant melanoma. As discussed in Section 2.2 and Section 3.3 of this report, this means that clinicians' first choice systemic treatment is expected to shift away from ipilimumab and towards pembrolizumab. Thus the outcome of this STA, which is necessarily focussed on ipilimumab as the prime comparator, is likely only to be most relevant to usual clinical practice in England for a limited period of time.

b) Data from three arms of two published clinical trials[19,22] provides a valid approximation to survival time profiles for patients treated with ipilimumab. Furthermore, this pooled dataset can be compared with the survival data collected during the OPTiM trial[4] for patients treated with T-VEC

The data pooled by the company in the development of a dataset for an ipilimumab comparator were derived from the ipilimumab plus DTIC arm of a trial that included only patients with previously untreated metastatic melanoma,[22] and also from the two ipilimumab arms (ipilimumab plus gp100, and ipilimumab monotherapy) of a trial that included only patients with previously treated metastatic melanoma.[19] This approach assumes that DTIC and gp100 are both ineffective, and that survival patterns are equivalent for patients treated with ipilimumab as first-line systemic therapy and patients for whom ipilimumab is administered subsequent to other treatment(s). The method of pooling used by the company involves calculating the combined mortality risk for separate arbitrary time periods across all of the trial arms being combined. This involves the assumption that censoring occurs at a constant rate within each time period for each of the data sets pooled and provides a reliable

approximation to full pooling. However, where possible, pooling should be carried out based on the K-M estimates using recorded patient event times.

c) The Korn proportional hazard model is an appropriate method for adjusting ipilimumab survival trends for differences in baseline patient characteristics between the ipilimumab trial data and the T-VEC data from the OPTiM trial[4]

The Korn model[51] was originally developed to help clinical researchers design new clinical trials of potentially promising treatments for patients with metastatic melanoma. Survival data were gathered from 70 individual trial arms from 42 separate Phase II trials relating to patients with stage IV disease in which the substances tested were deemed to be clinically ineffective. The Korn model was calibrated against these data, including only patients with stage IV disease. The ERG considers that this model is not appropriate for correcting the most important difference in prognostic factors between patients in the OPTiM trial[4] and patients in the ipilimumab trials.[19,22] In the OPTiM trial 54.7% of T-VEC patients had stage IIIB, stage IIIC or stage IV M1a disease compared with less than 20% in the ipilimumab trials.[19,22] In addition, the Korn data are dominated by the most seriously affected patient groups (stage IV M1b and stage IV M1c) rather than by stage IV M1a patients who are the only stage IV patients featured in the target subgroup of the OPTiM trial[4] for this appraisal. In previous NICE appraisals of ipilimumab (TA268[12] and TA319[11]), it was argued that that the use of the Korn model was appropriate as the trial populations consisted overwhelmingly of stage IV patients. However, this is not the case in this STA as the recommended treatment subgroup of the OPTiM trial[4] is restricted to patients with stage IIIB, stage IIIC and stage IV M1a disease.

d) The modified Korn model is superior to the original published Korn model

The unpublished modified Korn model was developed by the manufacturer of ipilimumab as an alternative to the original Korn model for use in the recent NICE appraisal of ipilimumab for patients with previously untreated metastatic melanoma (TA319[11]). There is no information in the public domain relating to the methods employed to modify the original model or to the data used to calibrate the modified model. However, it is reasonable to assume that the same, or similar, patient data were involved, and that therefore the problems already described (point c) regarding the use of the original Korn model are also valid for the modified version.

The modified Korn model includes five rather than four adjustment factors, adding elevated LDH whilst substituting a single ECOG variable (0 vs >0) in place of two ECOG variables

previously used (0 vs 1 vs 2+), alongside gender, visceral metastases and brain metastases. This alteration has the effect of placing a high weight on LDH status, but reducing the influence of gender, visceral metastases and ECOG PS. In the derivation of the AJCC 2009 melanoma staging classification,[1] elevated LDH was only considered relevant to patients with stage IV disease for whom it was found to be equivalent in effect to the most severe form of metastatic melanoma (non-pulmonary visceral stage IV M1c), so that any patient with distant metastases and elevated LDH is automatically assigned to the stage IV M1c category.

The company base case scenario only includes patients with stage IIIB, stage IIIC and IV M1a, so the new elevated LDH factor in the modified Korn model is irrelevant for this population. However, its calibration (based only on stage IV patients) has reduced the coefficients for the gender, ECOG and visceral metastases variables in the original equation. Thus the use of the modified Korn model introduces even greater uncertainty, and probable bias, than the original Korn model. The ERG therefore considers that the company's adjusted ipilimumab survival curves that employ the modified Korn model lack credibility.

e) An additional 'two-step' adjustment may also be necessary and appropriate

A further complication is presented by the possibility that the effectiveness of ipilimumab in the main trials[19,22] may vary significantly by stage of disease, so that a simple average effect over all trial patients may not adequately represent the true effectiveness of ipilimumab in a population similar to that enrolled in the OPTiM trial.[4] The company has attempted to correct for this additional case-mix imbalance by using a further application of the modified Korn model, resulting in a range of possible OS ipilimumab trends above and below the profile obtained by using the modified Korn model alone. Of course, the problems previously described are thereby confounded further, so that a very wide range of possible ipilimumab results is considered by the company to be feasible (and therefore a correspondingly wide range of incremental life years and QALYs have been generated).

f) PFS comparator data may be synthesised using the same modified Korn model as for OS

It is stated in the CS (page 89):

"In the absence of a Korn equation for PFS and the high correlation likely between PFS and OS, the same adjustments were applied to PFS."

However it is not the case that the multivariate model results reported in the Korn publication[51] are not available for PFS. In Table 2 of the published paper,[51] a full description is provided of a similar multivariate model for adjusting PFS data. The distributional model features three significant variables used to adjust for differences in baseline characteristics (PS 0/1/2+, gender and age). This PFS model is clearly quite different from the equivalent Korn OS model, the OS model in the modified Korn model and the two-step OS Korn model. In particular, it is noteworthy that where the same factors are present in both the Korn OS and PFS models, the estimated coefficient values are substantially lower in the PFS model than in the OS model.

The ERG therefore concludes that the company's use of the same OS modified Korn model for both OS and PFS is inappropriate and is likely to lead to misrepresentation of estimated PFS trends for ipilimumab and substantial additional uncertainty in estimated model outcomes, which in turn will affect the balance between survival time spent in the PFS and progressed health states.

ERG summary

The company is to be complemented for their thorough approach to the problem of defining a credible ipilimumab comparator from the available trial data. However, the difficulties associated with pooling data from very different clinical trials, and then applying multiple case-mix corrections in an effort to standardise published outcomes to the very different T-VEC population in the OPTiM trial,[4] serve only to demonstrate the very substantial uncertainty that attaches to the methods used and therefore to the outcome estimates obtained. The ERG concludes that the derived ipilimumab survival trends cannot be credited with any degree of reliability, and are an inadequate basis for estimating the cost effectiveness of T-VEC in the specified patient population, i.e. patients with non-visceral metastatic melanoma.

5.5.2 Lifetime survival projection for patients treated with T-VEC in the OPTiM trial

Within the company model different methods are applied sequentially to estimate OS over a period of 30 years from randomisation into the OPTiM trial.[4] The four phases, which are also displayed in Figure 8 are as follows:

- **Phase 1a (weeks 1-177)**: direct use of results from K-M analysis of the OPTiM trial[4] data
- **Phase 1b (weeks 178-269)**: estimated OS based on an exponential projection model developed by the company (no details are provided in the CS)
- **Phase 2 (weeks 270-520)**: estimated OS based on survival trends calculated from case-mix adjusted published analyses of a patient registry used in the development of the AJCC staging classification system[1]
- **Phase 3 (weeks 521-1560)**: estimated OS based on applying age/sex adjusted life table mortality rates.

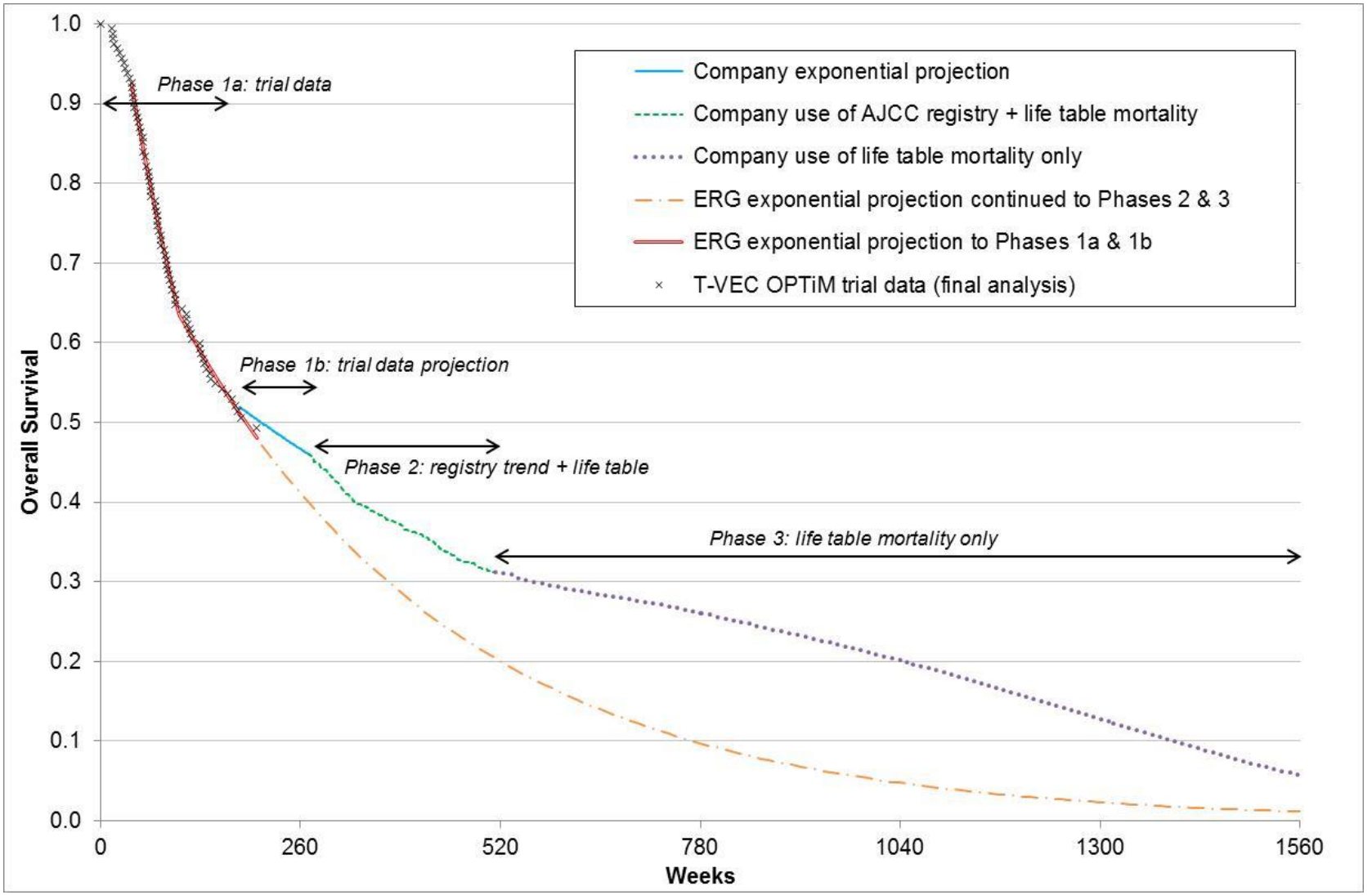


Figure 8 Company long-term T-VEC OS projection compared to ERG simple exponential alternative projection

It is generally appropriate to use K-M analysis results directly in a model prior to use of projection methods. However, in this case, it appears that the final analysis of the trial data (CS, Figure 4-6) has not been used in the model, which includes only OS data from the earlier, less mature, data cut. The ERG has carried out a curve-fitting exercise to a re-analysis of the final data cut which was requested during the clarification process. The ERG has found that a 2-part exponential model (Figure 9) closely follows the trial OS data from 9 months until the last recorded death (47 months).

It is noteworthy that the company model exponential trend (Phase 1b in Figure 8) deviates markedly from the final recorded trial data and leads to a clear separation from the exponential trend identified by the ERG. This results in a much more advantageous OS estimate for T-VEC compared to the long-term projection resulting from the fitted ERG curve (Figure 9).

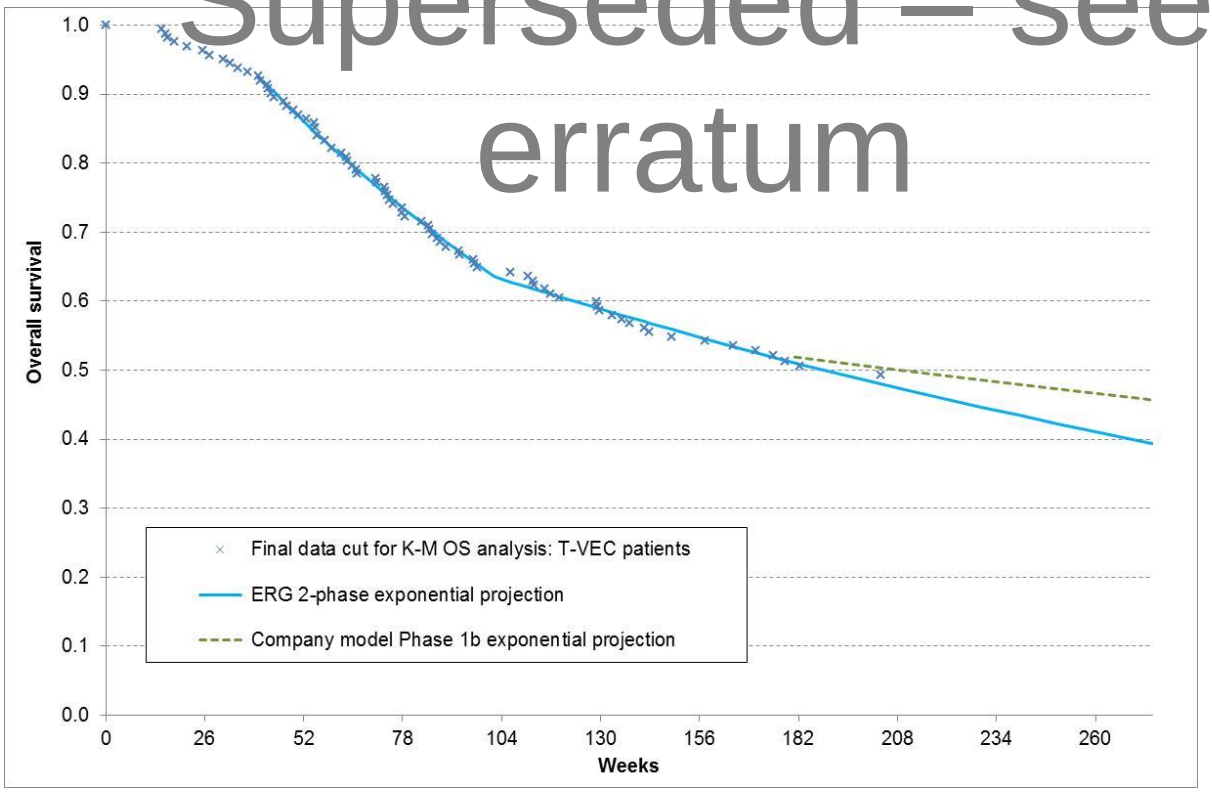


Figure 9 Comparison of company Phase 1b OS projection and ERG exploratory projection

In Phase 2, the company model uses a trend derived from published results of the analyses of patient registry data on which the AJCC staging classification[1] was based, with the addition of UK life table information[68] (though the exact nature of this adjustment has not been described in the CS). There are several difficulties with this method:

- The AJCC survival trends[1] only provide results for a maximum of 10 years from the date of diagnosis for patients with stage I to stage III disease, and from the recorded time of first distant metastases for patients with stage IV disease. Assuming that the submitted model uses a case-mix adjusted combination of AJCC[1] trends for stage IIIB, stage IIIC and stage IV M1a melanoma, the estimates used in the company model will mix patients at very different times in their disease career, starting from 0 to more than 20 years after first diagnosis. The relevance of such mixed AJCC[1] adjusted mortality estimates to the period up to 10 years from randomisation is highly questionable.
- The data on which the AJCC[1] analysis was performed were gathered prior to the current era of novel immunological treatments; these newer treatments have significantly altered the prospects for many patients. The AJCC[1] trends therefore probably represent a reasonable approximation to the prognosis of patients with access to only minimally effective treatments. The application of these data to extend the survival data in the OPTiM trial[4] implies that T-VEC has little or no continuing benefit after 5 years.
- The junction between Phase 1b and Phase 2 in the company model features a sudden increase in the mortality rate after exactly 270 weeks (62.1 months). However, there does not appear to be any clinical justification to support such a sudden change in the long-term mortality rate.
- For Phase 3, UK life table mortality rates[68] without adjustment, other than for age and sex, are applied within the company model. This implies that the remaining cohort of long-term survivors is at the same mortality risk as the general population. In effect, this means that the malignant melanoma suffered by all surviving patients is suddenly cured 10 years after entering the trial. The ERG is not aware of any evidence supporting such a claim.

ERG exploratory OS projections

The ERG has explored two approaches to the estimation of long-term OS for patients receiving T-VEC:

- Simple exponential modelling of the OPTiM trial[4] final data cut for T-VEC to 30 years (as shown in Figures 8 and 9).
- Modelling trends in PFS and post-progression survival (PPS) separately before combining the results to obtain an estimate for the mean OS.

Firstly, K-M analysis results for PPS in the OPTiM trial[4] (provided in response to an ERG clarification request) were reviewed and found to indicate that there is no basis for considering that after patients have suffered disease progression their future survival prognosis will be affected by prior treatment allocation. Therefore, the PPS data from both trial arms were pooled and re-analysed, resulting in a simple exponential (constant risk) model applicable to all progressed patients, with an expected mean PPS of 24.7 months.

ERG exploratory PFS projections

Analysis of the TTF data (as a proxy for PFS) from the final data cut from the OPTiM trial[4] revealed that a 2-phase exponential model accurately represented the trial data and provided an appropriate basis for projecting PFS in the T-VEC arm. In order to combine PFS and PPS it is necessary to exclude the portion of patients whose progression event was fatal (estimated as 4.8%) from the projected PPS component of the combined OS estimate.

Impact of ERG projections on the company's ICER

The importance of the problems identified by the ERG in relation to the company's approach to estimation of long-term survival in the T-VEC arm of the OPTiM trial[4] is most clearly seen in Figure 8 by considering the difference between the area under the survival curve in the company model after 30 years (108.5 months), the exploratory ERG OS exponential projection (73 months), and also the ERG PFS+PPS projection (68 months). The ERG's projections suggest that the company estimate for the mean OS of patients treated with T-VEC may be overstated by 49% to 59%. This will have a substantial effect on the model estimates of QALYs gained from treatment with T-VEC compared to any comparator, leading to sizeable increases in the size of estimated ICERs.

5.5.3 Issues related to ERG clarification questions

The responses provided to the ERG in respect of issues of concern with the company's cost effectiveness analysis are considered in this section.

Censoring of time to event data from the OPTiM clinical trial

The company provided the results of the requested re-analysis of OPTiM trial[4] data for OS, PFS (TTF) and PPS (ERG clarification question B-1), together with helpful graphical comparisons of K-M results for each outcome. These demonstrate that the censoring method has little effect on the survival time pattern for OS and PPS, which is to be expected as death is a 'hard outcome' and is generally reported rapidly. However, the PFS (TTF) results are markedly different indicating that informative censoring consistently understates PFS in each patient subgroup (Figures B-7, B-8 and B9 of the company response to ERG clarification questions). This is important for the decision model as it alters the balance of patients' projected time in PFS vs PPS, since PPS is calculated in the model as the difference between OS and PFS.

Adjustment anomaly in PFS estimation

The ERG identified an apparent anomaly in the CS (Figures 5-30 and 5-32), which appeared to show an unexpected alteration in the PFS profile of patients treated with T-VEC when the modified Korn model adjustment was active in the company model (ERG clarification question B-2). In response, the company explained that this change is not the direct effect of applying the modified Korn model adjustment (as it at first appeared to the ERG), but is due to the way subsequent registry data results were applied to both arms of the model, overriding the parametric model trends employed in the first phase of the model, which were found to be clinically implausible.

The ERG is grateful for the explanation of this anomaly, and acknowledges that the logic alteration is conservative. However, the ERG remains concerned that it can be seen as a strong indicator that the methods used to fit a parametric model to the trial PFS data are unreliable (clinically implausible), and that the correct approach would be to employ a more robust method for carrying out this analysis. The ERG PFS projective model described in Section 5.4.2 is a suitable alternative.

Time from diagnosis

The mean time from diagnosis to randomisation in the OPTiM trial[4] is greater than 3 years (Table B-5 of the company clarification response) with a standard deviation greater than 3 years. This is comparable with MDX010-20[19] in which the median time from diagnosis was 3.1 years, with a range from 0 to 38.9 years.[12] This confirms that the use of AJCC registry trends[68] up to 10 years from diagnosis (stage IIIB and stage IIIC patients) is inappropriate

when a substantial proportion of patients in one (MDX010-20[19]) of the two trials[19,22] that were pooled were already beyond the longevity limit of the AJCC data. This issue may also be true for the other ipilimumab trial (CA184-044[22]).

Ipilimumab acquisition cost per dose received

Ipilimumab treatment doses are calculated by patient body weight. The company provided mean body weight statistics for male and female patients who were randomised in the OPTiM trial[4] in response to an ERG clarification request.

A comparison with results reported from a survey of cancer patients in the UK[78] suggests that the North American population enrolled in the OPTiM trial[4] is generally heavier than the population typically treated in England and Wales. The UK study[78] showed that, across all types of adult cancer, the mean body weight in UK centres was 68.1kg for females and 77.1kg for males, whereas in the OPTiM trial[4] mean weight was 79.8kg for females, and 91.1kg for males.

Re-estimating the average cost per patient of treating English patients with ipilimumab, using separate male and female calculations results in a reduction in the drug acquisition cost of ipilimumab by 6.7%.

5.5.4 Other model issues

Discounting

The company model applies discounting to costs and outcomes on a continuous (weekly) basis, rather than annually in line with NHS budgeting and accounting years. This has the effect of reducing treatment acquisition and administration costs during the first year for both T-VEC and ipilimumab, as well as reducing the QALYs associated with both treatments. In particular, for those patients who continue on T-VEC treatment beyond 12 months, treatment costs are reduced from week 3 of year 1 instead of from the start of year 2.

Health state utility values

In the company's base case analysis, health state utility values are taken from the NICE appraisal of dabrafenib (TA321[14]) in preference to the values obtained by the company from a commissioned study[75] (CS, Appendix 1.7). It is the ERG's considered opinion that the values obtained from the commissioned study have greater face validity than those used in the base case analysis. In particular, the TA321[14] values poorly differentiate between distinct health states: there is no difference between values assigned to CR, PR and SD. Applying the commissioned study utility estimates reduces the number of incremental QALYs gained

by a small amount with a corresponding increase in the size of the estimated ICER per QALY gained.

Continuity correction

The company employs a half-cycle correction in their decision model for the estimation of outcomes and some costs. This method is recognised to be inaccurate except in particular circumstances. The ERG has applied the more generally applicable mid-cycle correction to the affected model outcomes. This results in a small decrease in the estimated incremental life years and QALYs gained, and a small increase in the estimated incremental costs per patient, so that the estimated ICER per QALY gained increases by a small amount.

Terminal disutility

The company model does not differentiate the estimated HRQoL applicable to patients in the PD state (which can last for an extended period) from the condition of patients in terminal care (usually considered as the last 2 weeks of life). Applying the utility value estimated in the commissioned utility study[75] (CS, Appendix 1.7) for the BSC state to the last 2 weeks of life results in a very small increase in the incremental QALYs gained from use of T-VEC, with a corresponding small reduction in the size of the estimated ICER per QALY gained.

Probabilistic ICER calculation error

An error has been identified in the method used by the company to calculate the probabilistic ICER per QALY gained. In the last stage of processing the PSA data, the ICER has been calculated as the simple average of 10,000 simulated ICERs, instead of as the ratio of the combined average of 10,000 incremental costs to the combined average of 10,000 incremental QALYs. This causes a bias in the value of the probabilistic ICER, so that the base case reported by the company (£1,647 per QALY gained) should in fact be £1,680 per QALY gained. This has no impact on the size of the estimated deterministic ICER.

5.6 Exploratory and sensitivity analyses undertaken by the ERG

In view of the serious problems identified by the ERG relating to the construction of an ipilimumab comparator for use in the company model, the ERG does not consider that any estimates of the cost effectiveness of T-VEC compared with ipilimumab in patients with non-visceral metastatic disease are reliable. Using different assumptions, widely differing estimated ICERs can be obtained, from T-VEC appearing to be dominant compared with ipilimumab (better outcomes at lower cost) to T-VEC appearing to be dominated by ipilimumab (poorer outcomes at higher cost), so that quoting any specific unreliable ICERs would be potentially misleading.

However, it is possible to offer a broad indication of the relative significance of the issues identified by the ERG:

- The company base case analysis uses the list price for ipilimumab and the proposed list price for T-VEC. Thus the current PAS price for ipilimumab is not applied. Results from the company model suggest that the estimated cost effectiveness of T-VEC is substantially worsened when using the reduced ipilimumab PAS price.
- Taken separately, the ERG approach to estimating OS and PFS have contrary effects on estimated cost effectiveness: the revised OS estimate appears to improve the position of T-VEC, whereas the revised PFS estimate worsens it.
- All of the other issues identified when considered individually have a very small impact on the position of T-VEC, generally increasing the size of the estimated ICER per QALY gained.
- When the PAS for ipilimumab is applied alongside the ERG's OS and PFS estimates, the ICER per QALY gained is very severely increased to a value far beyond the range normally considered acceptable.
- The cost effectiveness of T-VEC compared to ipilimumab varies from dominating (more effective at less cost in the modified Korn model) to being dominated (less effective at greater cost in the two-step Korn model).

5.7 Conclusions of the cost effectiveness section

In the absence of direct trial evidence for a clinically appropriate comparator, estimation of the relative cost effectiveness of T-VEC vs current clinical practice is rendered extremely difficult. The company's proposal for a constructed comparator, based on the pooling of data from two ipilimumab trials[19,22] adjusted for baseline characteristics and using a proportional hazard model derived from a patient population that is very different from the anticipated T-VEC licensed population, is considered by the ERG to be ill-conceived and unreliable as the basis for determining cost effectiveness. Moreover, due to the high degree of volatility exhibited in model-generated quantitative estimates of cost effectiveness when ERG amendments are implemented, the ERG does not consider that it is appropriate to present detailed alternative ICERs for this questionable comparison.

The ERG has also identified serious problems relating to the long-term projection of survival. These relate to the selective use of registry data and life table estimates. The company appeals to precedents from previous appraisals in melanoma to justify their approach to projecting survival. However, the ERG considers that the populations studied previously differ substantially from the target population proposed for T-VEC and from the population on which the Korn model[51] was based, so that the appeal to such precedents is not appropriate.

Had the OPTiM trial[4] included an alternative treatment arm involving a recognised alternative treatment (e.g. DTIC), then indirect evidence synthesis may have been appropriate. Unfortunately, it is not possible to determine whether GM-CSF constitutes an active or inactive comparator for T-VEC, so the data from the comparator arm of the OPTiM trial[4] can play no part in assessing the extent to which T-VEC benefits patients with non-visceral metastatic disease compared to current practice.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

As concluded in Section 5.7, due to the issues associated with T-VEC data and the method employed to construct a synthesised ipilimumab comparator, the ERG does not consider that it is appropriate to present detailed alternative ICERs for T-VEC vs ipilimumab.

7 END OF LIFE

The company has not made a case for T-VEC to be considered under NICE's End-of-Life criteria.

8 DISCUSSION

Evidence from the OPTiM trial

T-VEC is expected to be licensed for the treatment of patients with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease. In practice, the melanoma must also be injectable. Evidence for the efficacy of T-VEC treatment in this population has been obtained from a post-hoc analysis of data from patients with non-visceral metastatic disease who took part in the OPTiM trial[4].

The ERG considers that the efficacy results for the OPTiM trial[4] ITT population (a broader patient population that also includes patients with stage IV M1b and stage IV M1c disease), all of which favour T-VEC, may be subject to bias. This is because the trial lacked blinding, employed limited central assessment and the proportion of patients dropping out of the GM-CSF arm was higher than that associated with the T-VEC arm. All of these limitations also apply to the analyses carried out on data collected from the subgroup of patients with non-visceral metastatic melanoma, with the additional concern that these analyses were not pre-specified. The ERG notes that, for this non-visceral metastatic disease subgroup, the differences in treatment effect between the two trial arms, for all efficacy outcomes, were large. This suggests that, despite the identified limitations, for these patients, the conclusion that T-VEC is a more efficacious treatment option than GM-CSF may be credible. However, the ERG has concerns relating to the validity of this subgroup as it comprises both patients with stage III and stage IV disease. This is of concern as it is likely that the disease trajectory of patients differs by stage of disease which means this is not a relatively homogeneous patient group.

In summary, results from the OPTiM trial[4] show that T-VEC is clinically superior to GM-CSF. However, GM-CSF is not used in the NHS to treat patients with melanoma and, therefore, for the purposes of this STA, is not considered to be a relevant comparator

Applicability of the OPTiM trial results to clinical practice

The ERG considers that the characteristics of patients included in the OPTiM tria,[4] with non-visceral metastatic disease, are generally similar to the patient population likely to be considered for treatment with T-VEC in clinical practice in England. In this respect, the results from the OPTiM trial[4] are generalisable to patients seen in clinical practice in England.

Results from the OPTiM trial[4] show that, for patients treated with T-VEC, measures of ORR, DRR and TTF were better in the subgroup of patients with non-visceral metastatic disease

than in the whole trial arm: 40.5% vs 26.4%, 25.2% vs 16.3% and 13.1 months vs 8.1 months respectively. In addition, the results of an analysis conducted by the FDA,[37] of data from the subgroup of patients with non-visceral metastatic disease, suggest that patients who had very small lesions (<1cm2) were more likely to respond to T-VEC than the overall population: 30.4% vs 10.1% respectively. It is, therefore, possible that lesion size is also related to clinical effectiveness.

Survival results from the OPTiM trial[4] show that, for patients treated with T-VEC, OS benefit is extended further in the subgroup of patients with non-visceral metastatic melanoma than it is in the whole trial arm: 46.8 months vs 23.3 months respectively.

Results from the OPTiM trial[4] also suggest that T-VEC is a relatively safe treatment option. The most common AEs were flu-like symptoms. Patients experienced relatively few treatment-related Grade 3 to 5 AEs, treatment related SAEs or AEs leading to treatment discontinuation. However, evidence describing the effects of long-term exposure to T-VEC is currently limited, as is the extent of the risk of infection transmission from patients to close contacts or carers (T-VEC is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding). The safety profile of T-VEC is considered to compare favourably to the safety profiles of other currently available treatment options.

Comparison of T-VEC with relevant treatment options

The relevant comparators specified in the NICE scope and included in the company's decision problem were ipilimumab, vemurafenib and dabrafenib. Ipilimumab was considered by the company to be the primary comparator. In late 2015, NICE recommended that pembrolizumab should be made available for the treatment of NHS patients with malignant melanoma (both those previously treated,[15] and those who had not been previously treated,[16] with ipilimumab). The ERG's expert clinical advisor has suggested that clinicians may now shift from prescribing ipilimumab to prescribing pembrolizumab, making the latter the most appropriate alternative treatment for the majority of patients for whom treatment with T-VEC is being proposed. The ERG recognises, however, that pembrolizumab was not recommended by NICE at the time when the company produced its submission.

The only published trial results describing the efficacy of any treatment for patients with non-visceral metastatic melanoma are those from the OPTiM trial;[4] in this trial, these patients constituted 57% of the overall trial population. Relevant trials[17-22] assessing the efficacy of other currently recommended treatments by NICE,[11-16] only include relative few patients with non-visceral metastatic disease, fewerthan 20% of included patients. No subgroup analyses were conducted for this specific patient population in any of these trials.

As there was insufficient trial evidence to allow the efficacy of T-VEC to be compared with any of the comparators listed in the NICE scope, the company, after exploring a number of alternative methods, determined that the best approach was to generate a synthesised ipilimumab comparator using either the modified Korn model or the two-step Korn model. However, the ERG also considers that neither the modified Korn model nor the two-step Korn model enables a robust ipilimumab comparator to be created.

Currently, for a small proportion of patients with metastatic non-visceral melanoma seen in NHS clinical practice, a 'wait and watch' policy (in which no treatment is offered) is employed. Such a policy is likely to be favoured for the treatment of patients for whom the potential side-effects from immunotherapy outweigh the potential benefits from treatment. The ERG is not aware of any relevant trials of a 'wait and watch' policy. It may be that the results from the GM-CSF arm of the OPTiM trial[4] are similar to those expected from a 'wait and watch' policy as GM-CSF is not thought to be an active cancer treatment. However, although GM-CSF is not a recognised cancer treatment it is, nevertheless, not the same as 'no treatment'. For a minority of patients in the OPTiM trial,[4] improved outcomes were observed for some patients treated with GM-CSF. Furthermore, some Grade 1 and 2 AEs were associated with GM-CSF treatment, most notably fatigue and injection-site erythema. A 'wait and watch' policy would not be expected to result in improved outcomes, nor would such an approach be expected to result in AEs.

Expert advice to the ERG has highlighted that there is a very small group of patients with injectable non-visceral metastatic melanoma for whom treatment with an immunotherapy is not appropriate. This group includes patients with auto-immune diseases, such as rheumatoid arthritis, and those with inflammatory diseases, such as ulcerative colitis. Furthermore, the ERG has received clinical advice which suggests that for many patients in clinical practice, the most appropriate comparators to T-VEC are either isolated limb perfusion or electrochemotherapy, rather than an immunotherapy or a BRAF inhibitor.

Patient experience of injectable treatments is not discussed in the CS. The ERG is not confident that all patients with injectable melanoma will be accepting of this type of treatment every 2 weeks over a long period of time.

Appropriate line of treatment for T-VEC

The OPTiM trial[4] included a mix of patients treated in the first-line setting and those receiving T-VEC as a later line of treatment. Results for this mixed cohort are presented in the CS and the company model does not differentiate by line of treatment. It is, however, stated in the draft EPAR[5] that the efficacy of T-VEC can only be considered established in the first-line setting. In the FDA briefing document[37] it is suggested that the overall risk-benefit profile of

T-VEC shows most benefit to patients receiving first-line treatment. Furthermore, within the draft SmPC,[36] there is a caution that the efficacy data supporting the use of T-VEC in second or later line treatment settings are limited.

The lack of confidence in the efficacy of T-VEC as a second (or later) line of treatment is largely due to the fact that, during the period when the OPTiM trial[4] was conducted, first-line treatment options for patients were different from those available to such patients today. This means that the patients in the OPTiM trial[4] who received T-VEC as a second- (or later) line of treatment will be different from the patients receiving T-VEC as a second- (or later) line of treatment in clinical practice today. In addition, it is reported in the draft EPAR[5] that there is a strong correlation between line of therapy and disease stage; line of therapy was not retained as an independent predictor for DR in a multivariate analysis considering disease stage.

Treatment with T-VEC can be continued even if there is some evidence of disease progression, with a minimum of 6 months of treatment being recommended. The EMA[5] raised concern that, for some patients, next-line treatment may commence later than if an alternative to T-VEC had been administered at the time of disease progression. The ERG considers that, because injectable melanoma entails lesions that can be clearly seen by the treating clinician, unnecessary treatment delays are unlikely since, if there is evidence of rapid progression, clinicians would not delay next-line treatment in clinical practice.

Company's cost effectiveness estimates

The ERG does not consider that the cost effectiveness results presented by the company are reliable. The reasons that support this conclusion relate primarily to the clinical evidence employed within the model and the methods used in the company model to project survival.

There are four main clinical issues that cast doubt on the reliability of the company's cost effectiveness results. The first issue is whether ipilimumab is the most appropriate comparator to include in the company's baseline cost effectiveness analysis. The second and third issues relate to factors that affect patients' disease trajectory, namely (a) that the subgroup of patients with injectable non-visceral metastatic disease includes both patients with stage III and those with stage IV disease, and (b) that this subgroup includes both patients receiving T-VEC as a first-line treatment and those receiving it as a later line of treatment. The fourth issue is that the relative clinical effectiveness of T-VEC compared with any treatment currently used in clinical practice is unknown.

The methods employed within cost effectiveness models to project survival (PFS and OS) have a major influence on the magnitude of cost effectiveness results. The ERG considers

that the methods employed by the company to project OS for patients receiving T-VEC lack face validity. In addition, although the ERG commends the company on its endeavours to construct comparator data to enable the cost effectiveness of T-VEC to be compared with that of ipilimumab, the ERG does not consider that this synthesised comparator is sufficiently reliable to support a valid assessment.

The high degree of uncertainty associated with the model results is of particular concern to the ERG. When cost effectiveness estimates are generated using the company's synthesised ipilimumab comparators and the ERG's preferred OS and PFS projections for T-VEC (based on data from the OPTiM trial[4]), the cost effectiveness of T-VEC compared with ipilimumab varies from dominating (more effective at less cost in the modified Korn model) to being dominated (less effective at greater cost in the two-step Korn model).

Due to the issues relating to the clinical data, the absence of a credible comparator and the methods used by the company to project patient survival, the ERG does not consider that it is appropriate to present detailed alternative ICERs. However, results from exploratory analyses carried out by the ERG indicate that the 30-year mean survival for patients treated with T-VEC in the company model may be overstated by 49% to 59%, indicating the high level of uncertainty associated with the submitted cost effectiveness estimates.

9 OVERALL CONCLUSIONS

Results from the OPTiM trial[4] suggest that treatment with T-VEC is of superior efficacy to GM-CSF for a number of outcomes, including OS, in patients with injectable unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease. However, GM-CSF is not used in the NHS to treat patients with melanoma and, therefore, for the purposes of this STA, is not considered to be a relevant comparator. It has not been possible to obtain data that would allow the efficacy of T-VEC to be compared with any of the comparators currently used in NHS clinical practice to be undertaken with confidence.

The company has presented results that show the relative cost effectiveness of treatment with T-VEC compared with ipilimumab. However, the ERG considers that the company's synthesised comparator (created to represent the effectiveness of ipilimumab treatment) is ill-conceived and provides an unreliable basis for determining cost effectiveness. In addition, the ERG considers that serious issues relating to the methods employed in the company model to project long-term survival further reduce the reliability of the company's cost effectiveness results.

9.1 Implications for research

There has recently been a rapid increase in the number of drugs licensed (and recommended by NICE) to treat patients with malignant melanoma. Currently, the two most relevant comparators to T-VEC are pembrolizumab and ipilimumab. However, there is insufficient evidence available to allow a comparison of the efficacy of T-VEC to be made with either of these two drugs. Analyses, using data collected from patients with stage IIIB to stage IV M1a disease, included in both completed, ongoing and future trials assessing the efficacy of pembrolizumab and ipilimumab, would add to the evidence base. These analyses would be subject to limitations, namely that they would be an exploratory post-hoc subgroup comprising a mix of patients with stage III and stage IV disease and be undertaken in a small proportion of patients included in the trials. Thus the benefits of randomisation may be lost. Furthermore, not all patients would have injectable disease (the company estimates 73% of patients with stage IIIB to stage IV M1a have injectable disease). The analyses should include assessment of OS, PFS (and, where available, TTF) and ORR.

Data supporting the long-term safety of T-VEC treatment, including the potential for viral shedding, is currently lacking. This issue has, however, been addressed in the RMP agreed between the company and the EMA,[5] and post-marketing studies are being conducted to address this issue.

10 REFERENCES

1. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR*, et al.* Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27:6199-206.
2. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol. 2010; 28:3042-7.
3. Salama AK, de Rosa N, Scheri RP, Pruitt SK, Herndon JE, 2nd, Marcello J*, et al.* Hazard-rate analysis and patterns of recurrence in early stage melanoma: moving towards a rationally designed surveillance strategy. PloS one. 2013; 8:e57665.
4. Andtbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J*, et al.* Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015; 33:2780-8.
5. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) assessment report. Imlygic. 22 October 2015. Report No.: EMA/650948/2015.
6. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ*, et al.* Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011; 29:1239-46.
7. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. 2008; Available from: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp111.pdf (Accessed 02/12/2015).
8. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica. 2007; 92:1399-406.
9. Bedikian AY, Johnson MM, Warneke CL, Papadopoulos NE, Kim KB, Hwu WJ*, et al.* Does complete response to systemic therapy in patients with stage IV melanoma translate into long-term survival? Melanoma Res. 2011; 21:84-90.
10. Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A*, et al.* Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer. 2010; 46:270-83.
11. National Institute for Health and Care Excellence (NICE). Single technology appraisal for ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). 2014; Available from: https://www.nice.org.uk/guidance/ta319 (Accessed 02/12/2015).
12. National Institute for Health and Care Excellence (NICE). Single technology appraisal for ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). 2012; Available from: https://www.nice.org.uk/guidance/ta268 (Accessed 27/05/2015).
13. National Institute for Health and Care Excellence (NICE). Single technology appraisal for vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma (TA269). 2012; Available from: https://www.nice.org.uk/guidance/ta269 (Accessed 01/06/2015).
14. National Institute for Health and Care Excellence (NICE). Single technology appraisal for dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive

melanoma (TA321). 2014; Available from: https://www.nice.org.uk/guidance/ta321 (Accessed 27/05/2015).

15. National Institute for Health and Care Excellence (NICE). Single technology appraisal for pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). 2015; Available from: https://www.nice.org.uk/guidance/ta357 (Accessed 02/12/2015).

16. National Institute for Health and Care Excellence (NICE). Single technology appraisal for pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). 2015; Available from: https://www.nice.org.uk/guidance/ta366 (Accessed 02/12/2015).

17. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, *et al.* Improved survival with vemurafenib in melanoma with $BRAF^{V600E}$ mutation. N Engl J Med. 2011; 364:2507-16.

18. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380:358-65.

19. 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; 363:711-23.

20. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, *et al.* Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015; 16:908-18.

21. 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; 372:2521-32.

22. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011; 364:2517-26.

23. Sullivan RJ, Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. Eur J Cancer. 2013; 49:1297-304.

24. National Institute for Health and Care Excellence (NICE). Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma: NICE interventional procedure guidance [IPG446]. 2013; Available from: https://www.nice.org.uk/guidance/ipg446 (Accessed 14/01/2016).

25. National Institute for Health and Care Excellence (NICE). Interventional procedure overview of electrochemotherapy for melanoma metastases in the skin 2012; Available from: http://www.nice.org.uk/guidance/GID-IP1041/documents/electrochemotherapy-for-metastases-in-the-skin-of-nonskin-origin-and-melanoma-overview2 (Accessed 14/01/2016).

26. Byrne CM, Thompson JF, Johnston H, Hersey P, Quinn MJ, Michael Hughes T, *et al.* Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). Melanoma Res. 2005; 15:45-51.

27. Gaudy C, Richard MA, Folchetti G, Bonerandi JJ, Grob JJ. Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma. J Cutan Med Surg. 2006; 10:115-21.

28. Campana LG, Mocellin S, Basso M, Puccetti O, De Salvo GL, Chiarion-Sileni V, *et al.* Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Ann Surg Oncol. 2009; 16:191-9.

29. Heller R, Jaroszeski MJ, Reintgen DS, Puleo CA, DeConti RC, Gilbert RA*, et al.* Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. Cancer. 1998; 83:148-57.

30. Marty M, Sersa G, Garbay JR, Gehl J, Collins CG, Snoj M*, et al.* Electrochemotherapy – An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. Eur J Cancer Suppl. 2006; 4:3-13.

31. Mir LM, Glass LF, Sersa G, Teissie J, Domenge C, Miklavcic D*, et al.* Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. Br J Cancer. 1998; 77:2336-42.

32. Quaglino P, Mortera C, Osella-Abate S, Barberis M, Illengo M, Rissone M*, et al.* Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Ann Surg Oncol. 2008; 15:2215-22.

33. Kis E, Olah J, Ocsai H, Baltas E, Gyulai R, Kemeny L*, et al.* Electrochemotherapy of cutaneous metastases of melanoma--a case series study and systematic review of the evidence. Dermatol Surg. 2011; 37:816-24.

34. National Cancer Institute. Cancer Vaccines. Available from: http://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet (Accessed 17/12/2015).

35. Cancer Research UK. Melanoma Vaccines. Available from: http://www.cancerresearchuk.org/about-cancer/type/melanoma/treatment/melanoma-vaccines (Accessed 17/12/2015).

36. Amgen. Talimogene laherparepvec - EU summary of product characteristics. 2015.

37. US Food and Drug Administration (FDA). FDA Briefing Document: Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting. April 29, 2015. BLA 125518 talimogene laherparepvec (Amgen). Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM444715.pdf (Accessed 02/12/2015).

38. Bartlett DL, Liu Z, Sathaiah M, Ravindranathan R, Guo Z, He Y*, et al.* Oncolytic viruses as therapeutic cancer vaccines. Molecular Cancer. 2013; 12:103.

39. Senzer NN, Kaufman H, Amatruda T, Nemunaitis M, Daniels G, Glaspy J*, et al.* Phase II clinical trial with a second generation, GM-CSF encoding, oncolytic herpesvirus in unresectable metastatic melanoma. J Clin Oncol. 2009; 27:5763-71.

40. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M*, et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014; 371:1867-76.

41. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD*, et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015; 373:23-34.

42. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J*, et al.* Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014; 371:1877-88.

43. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D*, et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015; 372:30-9.

44. Amgen. Product: Talimogene Laherparepvec. Clinical Study Report: 005/05. Date: 14 April 2014.

45. Amgen. Product: Talimogene Laherparepvec. Clinical Study Report: 005/05 Final Analysis. Date: 23 February 2015.

46. BioVex Inc. Statistical Analysis Plan: A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX^{GM-CSF} Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease (up to and including Amendment 4, 04 January 2013).

47. BioVex Inc. Clinical Study Protocol: A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX^{GM-CSF} Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease (up to and including Amendment 5, 04 January 2013).

48. Kaufman HL, Andtbacka RHI, Collichio FA, Amatruda T, Senzer NN, Chesney J*, et al.* Primary overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. J Clin Oncol. 2014; 32(suppl; abstr 9008a).

49. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS*, et al.* Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012; 15:940-7.

50. Caro JJ, Ishak KJ. No head-to-head trial? Simulate the missing arms. Pharmacoeconomics. 2010; 28:957-67.

51. Korn EL, Liu P-Y, Lee SJ, Chapman J-AW, 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; 26:527-34.

52. Agarwala SS, Keilholz U, Gilles E, Bedikian AY, Wu J, Kay R*, et al.* LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). Eur J Cancer. 2009; 45:1807-14.

53. Fleeman N, A B, Beale S, Boland A, Dickson R, Richardson M*, et al.* Dabrafenib for the treatment of unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma[ID605]: A Single Technology Appraisal. 2014; Available from: http://www.nice.org.uk/guidance/ta321/documents/melanoma-braf-v600-unresectable-metastatic-dabrafenib-id605-evaluation-report2. Accessed 12 Nov 2014.

54. Merck Sharp & Dohme. Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab [ID760]: Company submission to NICE. 2015.

55. Scottish Medicines Consortium (SMC). ipilimumab (Yervoy®) 5mg/mL concentrate for solution for infusion: SMC No. (779/12). 2012; Available from: https://www.scottishmedicines.org.uk/files/advice/DAD_ipilimumab_Yervoy_FINAL_April_2012_for_website.pdf (Accessed 05/01/2016).

56. Scottish Medicines Consortium (SMC). ipilimumab 5mg/mL concentrate for solution for infusion (Yervoy®): SMC No. (997/14). 2014; Available from: https://www.scottishmedicines.org.uk/files/advice/ipilimumab_Yervoy_FINAL_Oct_2014_Amended_24.10.14_for_website.pdf (Accessed 05/01/2016).

57. Scottish Medicines Consortium (SMC). dabrafenib, 50mg and 75mg hard capsules (Tafinlar®): SMC No. (No.1023/15) 2015; Available from:

https://www.scottishmedicines.org.uk/files/advice/dabrafenib_Tafinlar_FINAL_February_2015_Amended_04.03.15_for_website.pdf (Accessed 05/01/2016).

58. Scottish Medicines Consortium (SMC). vemurafenib 240mg film-coated tablet (Zelboraf®): SMC No. (792/12). 2013; Available from: https://www.scottishmedicines.org.uk/files/advice/vemurafenib__Zelboraf__RESUBMISSION_FINAL_Nov_2013_for_Website.pdf (Accessed 05/01/2016).

59. Park NR, Lee SH, Kim J, Son SK, Seo HJ, Park DA. Cost-utility analysis of dabrafenib/trametinib combination (D plus T) for Brafv600 mutation-positive metastatic melanoma (MM) from the United Kingdom (UK) National Health Service (NHS) perspective. Value Health. 2014; 17:A71-A.

60. Lee D, Winn B, Lebmeier M, Batty A. Modelling the cost-effectiveness of ipilimumab for previously-treated, metastatic melanoma. Value Health. 2012; 15:A423-A.

61. Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L*, et al.* Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015; 33:1191-6.

62. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS, Investigators MDX. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013; 119:1675-82.

63. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S, Investigators MDX. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol. 2013; 24:2694-8.

64. Harvey B, Lee D, Gaudin A-F, Gueron B, Bregman B, Lebbe C*, et al.* Changes in the quality of life of advanced melanoma patients after 12 weeks of treatment with ipilimumab compared to gp100 in a phase III clinical trial. J Clin Oncol. 2013; 31.

65. Amgen. Clinical Study Protocol: A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease. 2013.

66. Bristol‑Myers Squibb. Yervoy (ipilimumab) EU Summary of product characteristics. 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf (Accessed 25/11/2015).

67. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013; Available from: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf (Accessed 01/06/2015).

68. Office for National Statistics. Interim Life Tables 2011-2013. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables (Accessed 30/11/2015).

69. Amgen. Data on file: costing the treatment pathway in advanced melanoma. 2014.

70. British National Formulary. BNF online. 2015; Available from: http://www.bnf.org/products/bnf-online/ (Accessed 15/01/2016).

71. Department of Health. National schedule of reference costs 2013/2014. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 (Accessed 01/06/2015).

72. Bell M, Wolowacz S. Resource Use and Costs Associated With the Administration of T-VEC in Patients With Unresectable Advanced Melanoma. Final Report. RTI-HS Project No. 0303954. Manchester: RTI Health Solutions 2015.

73. Johnston K, Levy AR, Lorigan P, Maio M, Lebbe C, Middleton M*, et al.* Economic impact of healthcare resource utilisation patterns among patients diagnosed with advanced melanoma in the United Kingdom, Italy, and France: results from a retrospective, longitudinal survey (MELODY study). Eur J Cancer. 2012; 48:2175-82.

74. Lorigan P, Marples M, Harries M, Wagstaff J, Dalgleish AG, Osborne R*, et al.* Treatment patterns, outcomes, and resource utilization of patients with metastatic melanoma in the UK: the MELODY study. Br J Dermatol. 2014; 170:87-95.

75. Ngo K, Gijsen M, Manousogiannaki I, Aristides M, Papanicolaou S. A bespoke utility study for advanced melanoma. PRMA Consulting reference: 3249. Fleet, Hampshire: PRMA Consulting; 2014.

76. Personal Social Services Research Unit. Unit costs of health and social care. 2012; Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2012/ (Accessed 30/11/2015).

77. Addicott R, Dewar S. Improving choice at end of life : a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice programme in Lincolnshire. London: King's Fund; 2008.

78. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PloS one. 2010; 5.

11 APPENDICES

11.1 Treatment by subgroup interaction tests in OPTiM trial

Table 35 Treatment by subgroup interaction tests for DRR and OS in OPTiM trial (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) (stage IIIb / stage IIIc, stage IV M1a / M1b, stage IV M1c)	<0.0001	0.7500	0.1907	0.7500
Disease stage (CRF) (stage IIIb / stage IIIc, stage IV M1a, stage IV M1b, stage IV M1c)	<0.0001	0.8204	0.0719	0.7331
Disease stage (CRF) (early [stage IIIb / stage IIIc / stage IV M1a], late [stage IV M1b / stage IV M1c])	<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
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

11.2 Additional information on the modified Korn model and the two-step Korn model

The aim of applying the modified Korn model and the two-step Korn model was to derive an adjusted K-M curve for ipilimumab in relation to the K-M curves for T-VEC. The KM curves for T-VEC are those for OS and TTF (a proxy for PFS in this trial) in the T-VEC licensed population of OPTiM trial.[4] The K-M curves for ipilimumab OS and PFS are compared with these respective T-VEC K-M curves by applying data from the relevant ipilimumab trials into the modified Korn model and the two-step Korn model.

As outcomes were not specifically reported for patients with metastatic non-visceral disease in the ipilimumab trials,[19,22] the company had to estimate survival of ipilimumab patients in this subgroup. The modified Korn model attempts to do this by adjusting data for the patients treated with ipilimumab in the ipilimumab trials[19,22] by taking the five prognostic factors into consideration, i.e. the baseline data for these prognostic factors are entered into an equation.

As suggested by the name given to the two-step Korn model, there were two steps to this approach:

1. Adjust data for the comparator arms in the ipilimumab trials (i.e. gp100 and DTIC) by taking the same five prognostic factors into consideration as in the modified Korn model
2. Adjust the comparator arm data further by applying a hazard ratio (derived from one[19] of the two ipilimumab trials[19,22]) for ipilimumab vs the comparator in the subgroups of patients with metastatic non-visceral disease to estimate survival outcomes for ipilimumab in a population broadly equivalent to the T-VEC licensed population; this is in order to assume that that there is an interaction between ipilimumab and patients with non-visceral metastatic melanoma.

The company specified that studies to be used in the application of the Korn methodology had to be Phase III RCTs, which evaluated either T-VEC or ipilimumab (which the company states to be the primary comparator), and which reported OS data. From the ten RCTs[4,17-19,21,22,40-43] identified for the NMA, three RCTs[4,19,22] were identified which met the company's inclusion criteria (Table 36).

Table 36 List of studies included in the evidence base for the modified Korn and two-step Korn models

Study	Treatments	Patient population
OPTiM trial[4]*	T-VEC GM-CSF	Previously treated and untreated patients with stage IIIC to stage IV M1c disease
MDX010-20[19]	Ipilimumab monotherapy ipilimumab in combination with gp100 gp100	Previously treated patients with stage III or stage IV disease
CA184-024[22]	Ipilimumab + DTIC DTIC monotherapy	Previously untreated with stage III or stage IV disease

Bristol‑Myers Squibb=Bristol Myers Squibb; DTIC=dacarbazine; GM-CSF= granulocyte-macrophage colony-stimulating factor
*The company cites the primary reference for the OPTiM trial to be a 2014 conference abstract by Kaufman et al[48]
Source: CS, adapted from Table 4-22

11.2.1 The modified Korn model

The model originally reported by Korn[51] can be used to predict OS for melanoma patients using four prognostic characteristics; gender, ECOG PS, presence of visceral metastases, and presence of brain metastases. The coefficients for the effects of these variables on relative risk were obtained using prediction models based on individual patient data from 42 Phase II studies, in 2100 patients with metastatic melanoma, and are provided in Equation 1.

Equation 1)

$$\log(\widehat{HR}) = 0.248X_{Gender=Male} + 0.436X_{ECOG=1} + 0.948X_{ECOG\geq 2} \mp 0.421X_{Visceral=YES} + 0.304X_{Brain=YES}$$

The proportion of patients with each specified characteristic are inputted into the equation in order to give the log(HR) for each treatment group.

However, the company decided that a modified Korn model, which would take elevated LDH levels into consideration as a prognostic factor, was more appropriate to adjust the data as elevated LDH levels has been found to be an important independent prognostic factor in metastatic melanoma.[52] Bristol‑Myers Squibb developed such a model in their recent submission to NICE for the use of ipilimumab in previously untreated metastatic malignant melanoma.[11] The modified Korn equation with the estimated coefficients is:

Equation 2)

$$\log(\widehat{HR}) = -0.154X_{Gender=Female} - 0.400X_{ECOG=0} - 0.285X_{Visceral=NO} - 0.306X_{Brain=NO} - 0.782X_{LDH=Normal}$$

The company used the modified Korn-adjusted model to adjust OS and PFS for ipilimumab, so that the adjusted survival data represent survival for ipilimumab treated patients as if they had the patient characteristics of the T-VEC-licensed population. Although the Korn algorithm was developed for OS data, the company justify their use of the Korn algorithm for adjusting PFS data by stating that high correlation is likely to occur between PFS and OS.

The ERG also notes that where the company present PFS data for T-VEC from OPTiM trial,[4] they are actually presenting TTF, which was a secondary outcome of the OPTiM trial[4] (see Table 5 for definition). In the company's response to the ERG clarification letter, the company state that due to the mode of action of T-VEC, whereby responses may occur post-progression, PFS would not be a meaningful endpoint for the OPTiM trial[4] study.

Method

1. The company calculated log(HR)s for each of the T-VEC and ipilimumab trial arms, by inputting each treatment arm's baseline distribution values into *Equation 2*. The difference in log(HR)s for the T-VEC licensed population for OPTiM trial[4] and for the ITT population for the ipilimumab trials reflects the size of the difference in outcomes due to differences in patient populations.

2. An adjustment factor was estimated, which would could then be used to adjust the worse prognosis of patients in the ipilimumab trials to the baseline characteristics of the T-VEC licensed population in the OPTiM trial.[4] The lower the adjustment factor, the greater the upward adjustment in ipilimumab survival.

The adjustment factor was calculated using Equation 3:

Equation 3)

$$AF = \frac{HR_{TVEC_{baseline\ characteristics}}}{HR_{Comparator_{baseline\ characteristics}}}$$

AF=adjustment factor

The calculated HRs and adjustment factors are presented in Table 37.

Table 37 Model coefficients and adjustment factors for OS and PFS: modified Korn model

Study	Treatment (population)	HR equations	HR	Adjustment Factor
OPTiM trial[4]	T-VEC (stage IIIB to stage IV M1a)	Log(HR) = -0.154$X_{Gender=0.44}$ -0.400$X_{ECOG=0.74}$ -0.285$X_{visceral=1}$ -0.306$X_{Brain=1}$ -0.782$X_{LDH=0.94}$	0.18	NA
MDX010-20[19]	Ipilimumab (previously treated stage III to stage IV)	Log(HR) = -0.154$X_{Gender=0.41}$ -0.400$X_{ECOG=0.53}$ -0.285$X_{visceral=0.11}$ -0.306$X_{Brain=0.89}$ -0.782$X_{LDH=0.61}$	0.35	0.53
CA184-024[22]	Ipilimumab (previously untreated stage III to stage IV)*	Log(HR) = -0.154$X_{Gender=0.39}$ -0.400$X_{ECOG=0.71}$ -0.285$X_{visceral=0.17}$ -0.306$X_{Brain=0.99}$ -0.782$X_{LDH=0.63}$	0.31	0.60

*In the Bristol-Myers Squibb NICE submission for ipilimumab in previously untreated patients, an OS was derived for monotherapy ipilimumab at 3mg/kg for the previously untreated study population. The adjustment factor calculated in this analysis was applied to the derived OS data
HR=hazard ratio; NA=not applicable; OS=overall survival; PFS=progression free survival
Note: Time to treatment failure used as proxy for PFS for patients treated with T-VEC in OPTiM trial[4]
Source: CS, adapted from Table 4-24

3. Adjusted OS and PFS for ipilimumab were estimated by adjusting Kaplan-Meier curves [S(t)] using the adjustment factor, as shown below in Equation 4:

Equation 4)

$$S(t)_{NEW} = S(t)_{OLD}{}^{AF}$$

4. A 95% prediction about the adjusted OS estimates was calculated using standard errors provided in TA319 to calculate a 95% confidence interval for the HR.

5. As two curves were generated for ipilimumab, these were pooled using the modified Mantel-Haenszel method.

11.2.2 Two-step Korn model

The two step Korn model assumes that there is an interaction between ipilimumab and a population broadly equivalent to the T-VEC licensed population. In other words, this method assumes that the treatment effect of ipilimumab would be greater in a population broadly equivalent to the T-VEC licensed population than in the ITT population of the ipilimumab trials.

As outcomes were not specifically reported for a population broadly equivalent to the T-VEC licensed population in the ipilimumab trials, the company had to estimate survival of ipilimumab patients in this subgroup. The company's approach was to adjust data for the comparators in the ipilimumab trials (i.e. gp100 and DTIC) using the modified Korn model, which would take five prognostic factors into consideration, and then adjust the comparator arm data again by applying a HR (from one of the ipilimumab trials) for ipilimumab vs the comparator in a population broadly equivalent to the T-VEC licensed population to estimate survival outcomes for ipilimumab in a population broadly equivalent to the T-VEC licensed population.

Table 38 Hazard ratios reported in ipilimumab trials

Trial	ITT population type	ITT population HR (95% CI)	Earlier stage disease definition	Earlier stage disease HR (95% CI)
MDX010-20[19]	Previously treated patients	0.64 (0.49 to 0.84)	M0, M1a and M1b combined	0.47 (0.27 to 0.82)
CA184-024[22]	Previously untreated patients	0.72 (0.59 to 0.87)	M0 and M1a*	0.83* (not estimated)

* HR calculated based on the weighted average of HRs for M0 and M1a reported in CA184-024[22]
CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat
Source: CS, adapted from Table 4-25

Although the ipilimumab trials did not report data for the exact TVEC licensed population (stage IIIB to stage IV M1a, non-visceral metastatic disease subgroup) the company obtained HRs for ipilimumab vs the relevant comparator (i.e. gp100 or DTIC) in earlier stage disease subgroups as shown in Table 38. The HR obtained from the ipilimumab trial in previously treated patients was for the subgroup of M0, M1a and Mb stage patients. For the ipilimumab trial in previously untreated patients, the HR was obtained by calculating the weighted average of HRs for M0 stage and M1a stage subgroups. The company used the more conservative HR (0.47), assuming that ipilimumab would have a larger interaction effect in the T-VEC licensed population. The company notes that the HRs for the earlier disease stage subgroups are based on very small numbers; less than 20% of patients belonged to this subgroup in these trials. The company highlights that these small numbers render the estimate of interaction highly uncertain.

Method

1. The company calculated log(HR)s using the Korn equation (as before) for the T-VEC, gp100 and DTIC trial arms. The difference in log(HR)s for the T-VEC licensed population and ipilimumab trials ITT population reflects the size of the difference in outcomes due to differences in patient populations.

2. The company calculated the adjustment factor, which would could then be used to adjust the worse prognosis of patients in the gp100 and DTIC trial arms to the baseline characteristics of the T-VEC licensed population in the OPTiM trial.[4]

The adjustment factors were calculated using Equation 3:

Equation 3)

$$AF = \frac{HR_{TVEC_{baseline\ characteristics}}}{HR_{Comparator_{baseline\ characteristics}}}$$

AF=adjustment factor

The calculated HRs are presented in Table 39.

Table 39 Model coefficients and adjustment factors for OS and PFS: two-step Korn model

Study	Treatment (population)	HR equation	HR	Adjustment Factor
OPTiM trial[4]	T-VEC (stage IIIB to stage IV M1a)	Log(HR) = -0.154$X_{Gender=0.44}$ -0.400$X_{ECOG=0.74}$ -0.285$X_{visceral=1}$ -0.306$X_{Brain=1}$ -0.782$X_{LDH=0.94}$	0.18	NA
MDX010-20[19]	Ipilimumab (previously treated stage III to stage IV)	Log(HR) = -0.154$X_{Gender=0.41}$ -0.400$X_{ECOG=0.53}$ -0.285$X_{visceral=0.11}$ -0.306$X_{Brain=0.89}$ -0.782$X_{LDH=0.61}$	0.35	0.53
CA184-024[22]	Ipilimumab (previously untreated stage III to stage IV)	Log(HR) = -0.154$X_{Gender=0.39}$ -0.400$X_{ECOG=0.71}$ -0.285$X_{visceral=0.17}$ -0.306$X_{Brain=0.99}$ -0.782$X_{LDH=0.63}$	0.31	0.60

DTIC=dacarbazine; HR=hazard ratio; NA=not applicable; OS=overall survival; PFS=progression free survival
Note: Time to treatment failure used as proxy for PFS for patients treated with T-VEC in OPTiM trial[4]
Source: CS, adapted from Table 4-26

3. The company adjusted survival curves for gp100 and DTIC using the calculated adjustment factor, as shown in Equation 4, to reflect survival as if the gp100 and DTIC patients had the same baseline characteristics as the T-VEC patients:

Equation 4)

$$S(t)_{NEW} = S(t)_{OLD}{}^{AF}$$

4. The reported HR (0.47) for ipilimumab vs gp100 stage IIIB to stage IV M1a disease subgroup was applied to adjust gp100 outcomes to reflect outcomes for ipilimumab in this population. The company assume that the HR for ipilimumab compared to gp100 is fully adjusted and applies across different populations.

5. The company pool the two curves using the modified Mantel-Haenszel method to generate the estimated OS of ipilimumab.

11.2.3 Participant characteristics of studies included in application of both Korn models

The baseline characteristics of the participants in the T-VEC and ipilimumab trials are provided in Table 11. There were differences in terms of ECOG PS, LDH levels, and stage of metastases across trials, emphasising the importance of performing adjustments which take these prognostic factors into consideration. The company highlights that the T-VEC licensed population did not have visceral metastases (due to the earlier stage of disease within these patients), whereas 11% and 17% of patients in the two ipilimumab arms of the MDX010-20[19] and CA184-024[22] trials had no visceral disease.

Table 40 Comparison of patient baseline characteristics from OPTiM trial and ipilimumab trials MDX010-20 and CA184-024

Patient characteristic	OPTiM trial[4] stage IIIB to stage IV M1a disease (T-VEC, N=163)	OPTiM trial[4] ITT (T-VEC, N=295)	MDX010-20[19] (Ipilimumab, N=137)	CA184-024[22] (Ipilimumab, N=250)
Age	Median: 63.0	Median: 63.1	Mean: 56.8	Mean: 57.5
Gender (%)				
Male	56	59	59	61
Female	44	41	41	39
ECOG performance status (%)				
0	74	71	53	71
>=1	26	28	47	29
Unknown	1	1	0	0
No visceral disease (%)*	100	55	11	17
Stage of disease (%)†				
III	55	30	1	2
IV M1a	46	25	10	15
IV M1b	NA	22	16	26
IV M1c	NA	23	73	57
Unknown	0	<1		
Brain metastases (%)				
No	100	99	89	99
Yes	0	1	11	1
LDH (%)				
≤ULN	95	90	61	63
>ULN	1	5	39	37
Unknown	4	5	0	0

ECOG=Eastern cooperative oncology group; ITT=intention to treat; LDH=Lactate dehydrogenese; NA=not applicable; ULN=upper limit of normal

*Visceral disease defined as inclusion of stage IIIB to stage IV M1a and exclusion of stage IV M1b to stage IV M1c

† Values are rounded up to the nearest whole number and so may exceed 100%

Source: CS, adapted from Table 4-23

11.2.4 Risk of bias of included studies in application of both Korn models

The company's assessments of risk of bias for the OPTiM trial[4] have been reported in Section 4.2.5 (Table 8). The company's assessment of risk of bias for the ipilimumab trials presented in Appendix 1.4 of the CS (Table 1-26) is summarised in Table 41. As is evident, the ERG disagrees with the company that there is evidence to suggest that the authors measured more outcomes than they reported in these trials. From an examination of only the published papers for MDX010-20[19] and CA184-024,[22] the ERG does not believe there is any such evidence.

Table 41 Company's assessment of risk of bias for ipilimumab trials with ERG comments

Risk of bias criteria	Company assessment		ERG comment
	MDX010-20	CA184-024	
Was randomisation carried out appropriately?	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	Unclear	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Agree
Were there any unexpected imbalances in dropouts between groups?	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Yes	Disagree
Did the analysis include an intention-to-treat analysis? Was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Agree

Source: CS, appendix 1.4, adapted from Table 1-26

11.2.5 Results from the modified Korn model

The adjusted OS data from the modified Korn model are provided in Figure 10. The affect on the ipilimumab data is to increases median OS from 10.8 months to 21.3 months. This compares with a median OS for T-VEC of 46.8 months. Mean (calculated by finding the area under the curve [AUC]) and median OS results are tabulated in Table 42.

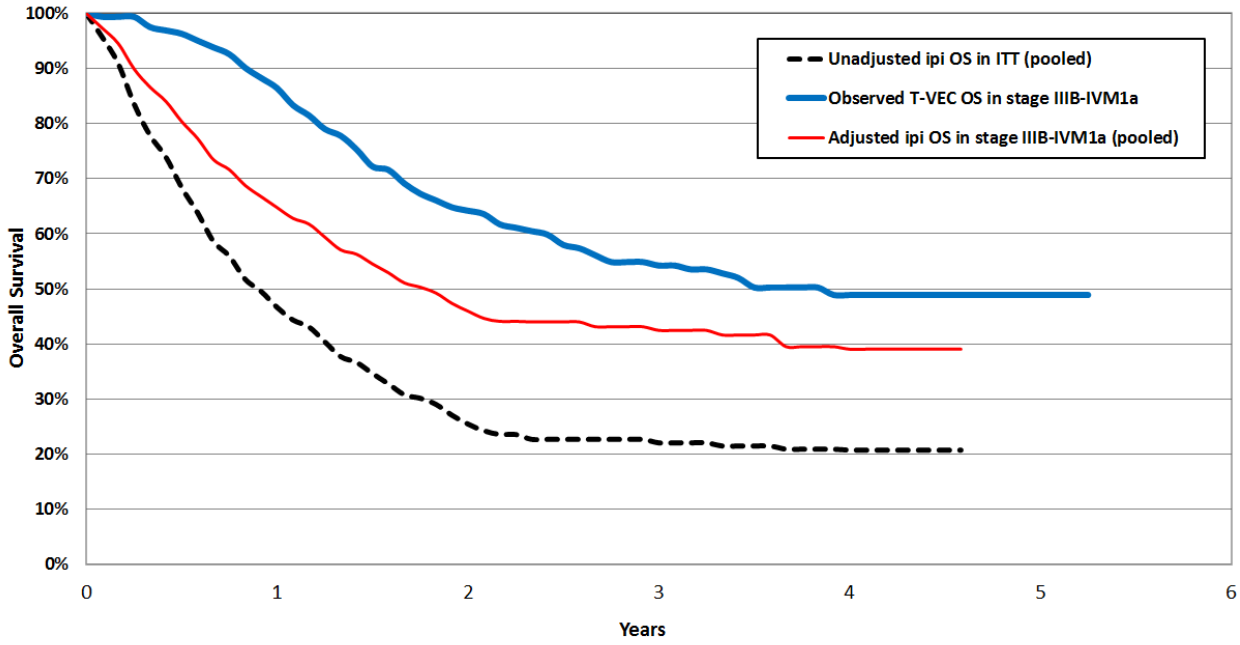


Figure 10 Modified Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

OS=overall survival; ipi=ipilimumab; T-VEC=talimogene laherparepvec
Source: CS, Figure 4-12

Table 42 Modified Korn model median and mean OS for ipilimumab in patients with stage IIIB to stage IV M1a disease

Median or mean	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
Source: Response to the ERG clarification letter, Table A-2

The adjusted PFS data using the modified Korn model are provided in Figure 11. The effect on the ipilimumab data is to increase median PFS from 2.8 months to 5.3 months. This compares with a median TTF (proxy for PFS) for T-VEC of 13.1 months. Mean (AUC) and median PFS results are tabulated in Table 43.

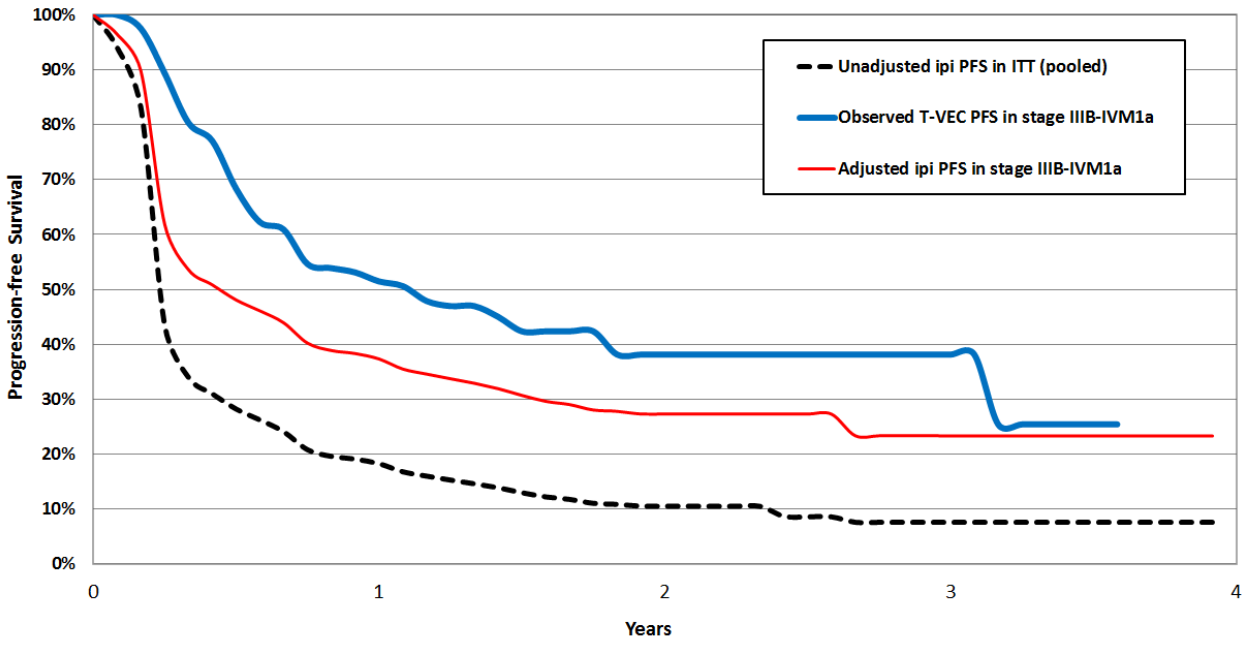


Figure 11 Modified Korn adjusted PFS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

Ipi=ipilimumab; PFS=progression free survival; T-VEC=talimogene laherparepvec
Source: CS, Figure 4-13

Table 43 Modified Korn model median and mean PFS for ipilimumab in patients with stage IIIB to stage IV M1a disease

Median or mean	Unadjusted OS	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
Note: Time to treatment failure used as proxy for PFS for patients treated with T-VEC in OPTiM trial[4]
Source: Response to the ERG clarification letter, Table A-3

The company also provided the 95% prediction interval about the adjusted ipilimumab curve, displaying the upper and lower limits for the adjusted ipilimumab curve, as shown in Figure 12. An upper limit for the median OS of ipilimumab was not reached, as the OS rate for the upper limit curve does not fall below 50%. The upper limit for ipilimumab OS suggests that T-VEC is initially more effective than ipilimumab, but in later years, the curves cross and that patients on ipilimumab may experience better OS rates than those on T-VEC. However, this would only be the case if ipilimumab OS is close to the upper limit of the estimated ipilimumab survival. The lower limit curve suggests that ipilimumab median survival may be as low as 14.6 months, in comparison to 46.8 months with T-VEC. Mean (AUC) and median OS results are tabulated in Table 44.

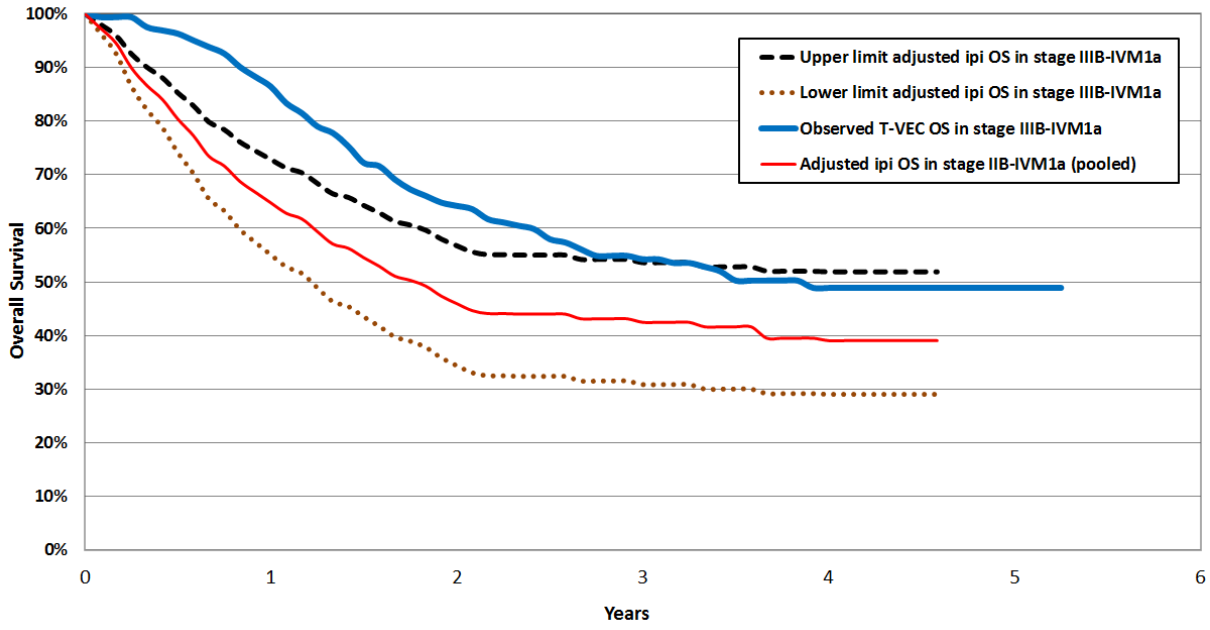


Figure 12 95% prediction interval around the modified Korn adjustment for ipilimumab OS

Ipi=ipilimumab; ITT=intention-to-treat; OS=overall survival; T-VEC=talimogene laherparepvec
Source: CS, Figure 4-14

Table 44 Prediction interval (95%) around the modified Korn adjustment for Ipilmumab OS

Median or mean	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
Source: Response to the ERG clarification letter, Table A-4

11.2.6 Results from applying the two-step Korn model

The adjusted OS data from the two-step Korn model are provided in Figure 13. The Korn adjustment to the ipilimumab data generates a survival curve which is comparable to that of T-VEC. Median OS was not reached for adjusted ipilimumab, as survival rates do not fall below 50%. The curves suggest that T-VEC is initially more effective than ipilimumab, but in later years, patients on ipilimumab may experience better OS rates than those on T-VEC. Overall, the results suggest that OS is comparable between T-VEC and ipilimumab even after applying the conservative two-step Korn model. Mean (AUC) and median OS results are tabulated in Table 45.

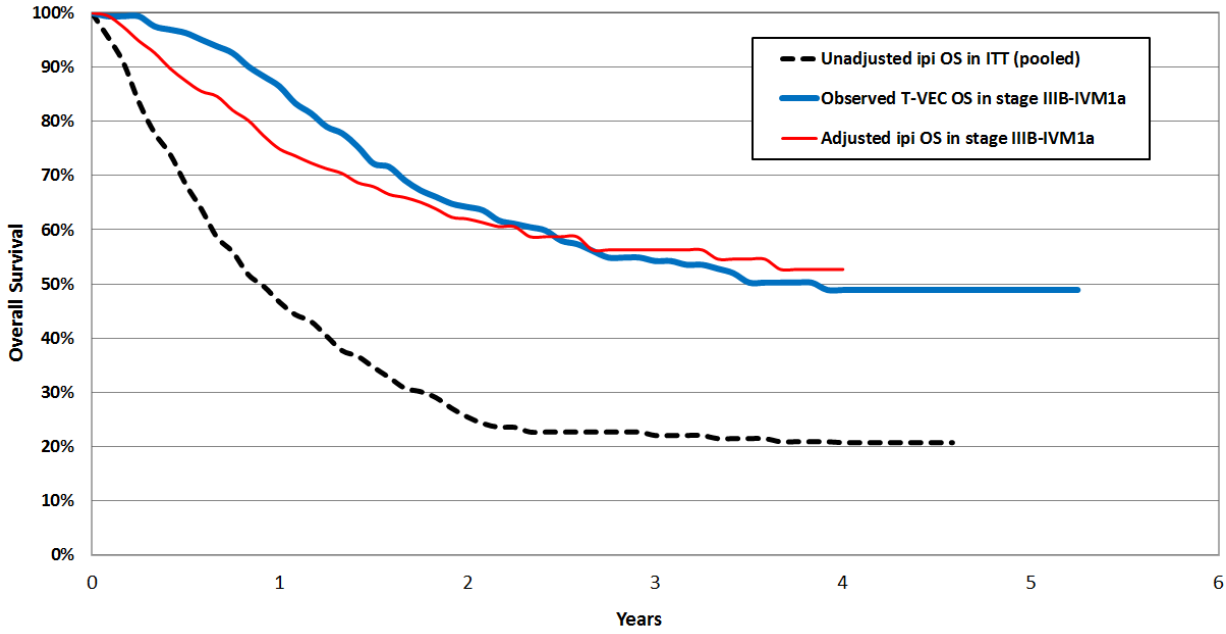


Figure 13 Two-step Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

Table 45 Two-step Korn model median and mean OS for ipilimumab in patients with stage IIIB to stage IV M1a disease

Median or mean	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; T-VEC=talimogene laherparepvec
Source: Response to the ERG clarification letter, Table A-5

The company also provided a figure with 95% prediction intervals around the two-step Korn model OS estimate for ipilimumab in their response to the ERG clarification questions which is provided in Figure 14. 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.

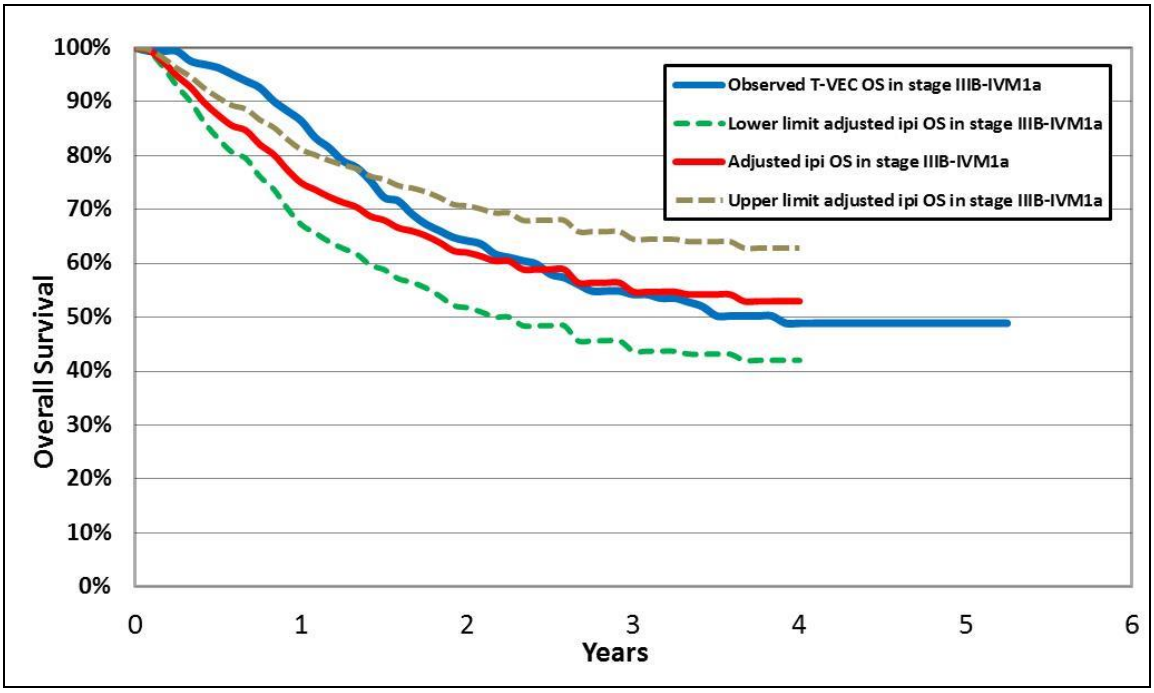


Figure 14 Two-step Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

Ipi=ipilimumab; OS=overall survival; T-VEC=talimogene laherparepvec.
Source: Response to the ERG's clarification letter, Figure A-2

Table 46 Two-step Korn adjusted median and mean OS for ipilimumab in patients with stage IIIB to stage IV M1a disease

Median or mean	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
Source: Response to the ERG's clarification letter, Table A-7

The adjusted PFS data from the two-step Korn model are provided in Figure 15. Median PFS was found to be greater for the adjusted ipilimumab data (17.6 months) than for T-VEC (13.1 months). Mean (AUC) and median PFS results are tabulated in Table 47.

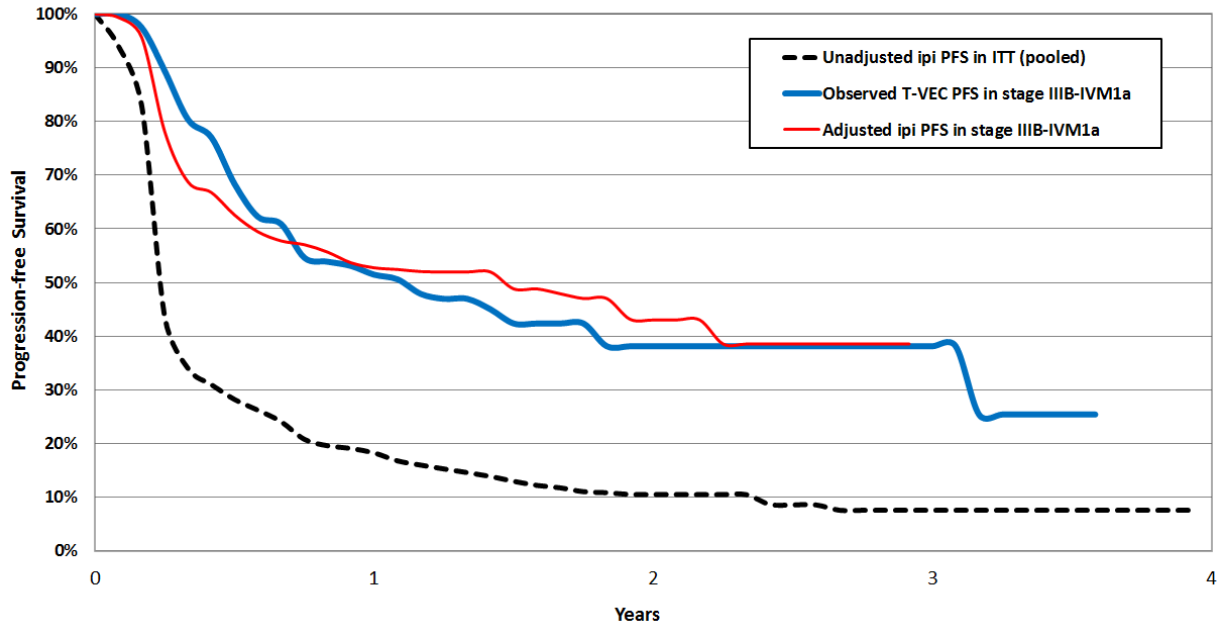


Figure 15 Two-step Korn model PFS curve for ipilimumab in patients with stage IIIB stage IV M1a disease

Ipi=ipilimumab; ITT=intention-to-treat; PFS=progression free survival; T-VEC=talimogene laherparepvec
Source: CS, Figure 4-16

Table 47 Two-step Korn model median and mean PFS for ipilimumab in patients with stage IIIB to stage IV M1a disease

Median or mean	Unadjusted OS	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
Source: Response to the ERG clarification letter, Table A-6
Ipi=ipilimumab; ITT=intention-to-treat; OS=overall survival; T-VEC=talimogene laherparepvec
Note: Time to treatment failure used as proxy for PFS for patients treated with T-VEC in OPTiM trial[4]
Source: Response to the ERG's clarification letter, Table A-6

11.2.7 Additional analysis requested by the ERG: inclusion of additional studies into modified Korn model

It was unclear to the ERG as to why the company did not include data from CheckMate 067 (a Phase III trial of nivolumab alone or combined with ipilimumab vs ipilimumab alone) and KEYNOTE 006 trials (a comparison of two different dosing schedules of pembrolizumab with ipilimumab alone) to obtain Korn-adjusted estimates of ipilimumab survival. The ERG therefore requested the company clarify this and perform additional analyses, if possible.

In the company's response to the ERG's clarification letter, the company confirmed that Checkmate 067 did not report OS data, and so it was not possible to include this study. The company also stated that KEYNOTE 006 was not included as OS data were immature data from an interim analysis.

Since OS data were reported in KEYNOTE 006, the company did nevertheless present the findings from the modified Korn model by including the data from the trial. These findings are presented in Figure 16 to Figure 17. In summary, the company noted that 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. These results were in accordance with those from the analysis which excluded KEYNOTE 006 data (Table 48 and Table 49).

The company stated it was not possible to implement the two-step Korn model by incorporating data from KEYNOTE 006 as the first step of the two-step Korn model requires RCTs with a non-active control group (to represent BSC); the company considers DTIC and gp100 to be non-active controls. As KEYNOTE 006 compared ipilimumab to the active comparator pembrolizumab, it was not possible to include KEYNOTE 006 data in the two step Korn model.

The ERG notes that the company assessed Checkmate 067 and KEYNOTE 006 to be at low risk of bias. Both studies performed ITT analyses, although the concealment of treatment allocation was judged to be unclear for both trials. Randomisation was carried out appropriately for KEYNOTE 006, however was judged unclear for Checkmate 067. Both studies blinded the care providers, participants and outcome assessors to treatment allocation. The ERG agrees with the company's risk of bias assessment for these two studies.

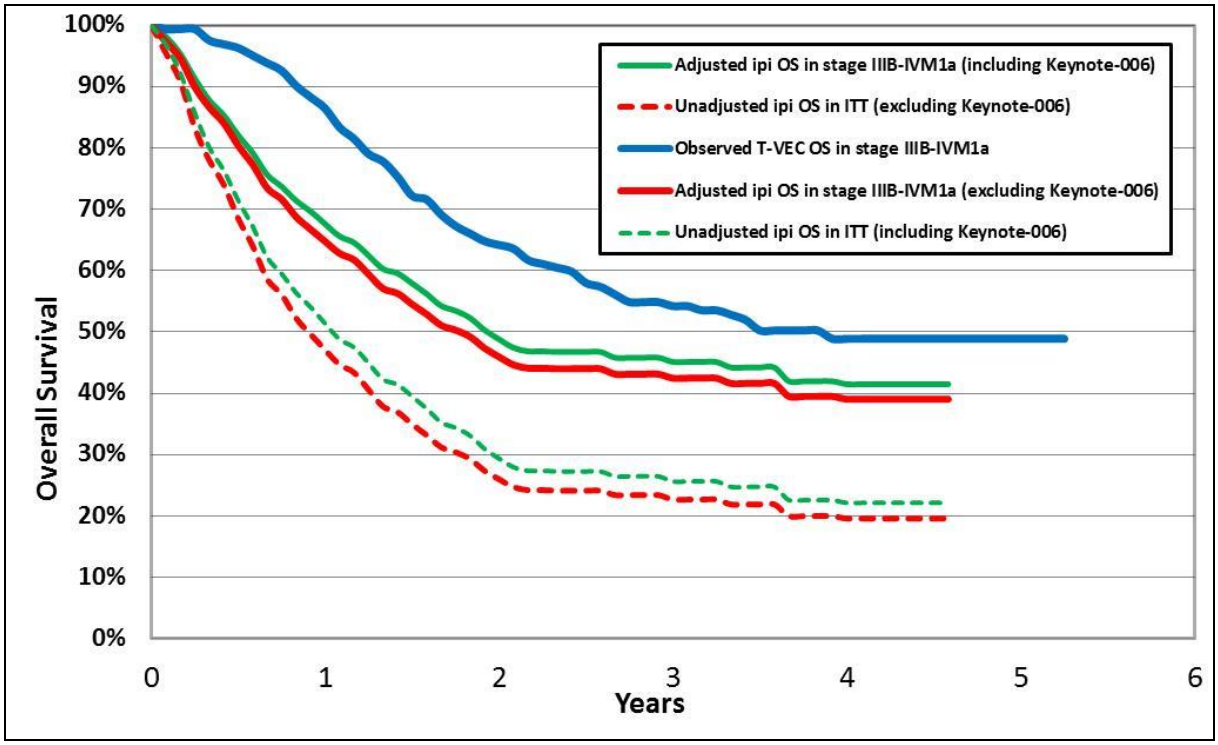


Figure 16 OS curves including KEYNOTE 006 trial using modified Korn model

Ipi=ipilimumab; ITT=intent to treat; OS=overall survival
Source: Response to the ERG's clarification letter, Figure A-4

Table 48 Median and mean OS including or excluding KEYNOTE 006 using modified Korn model

Median or mean	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
Source: Response to ERG's clarification letter, Table A-8

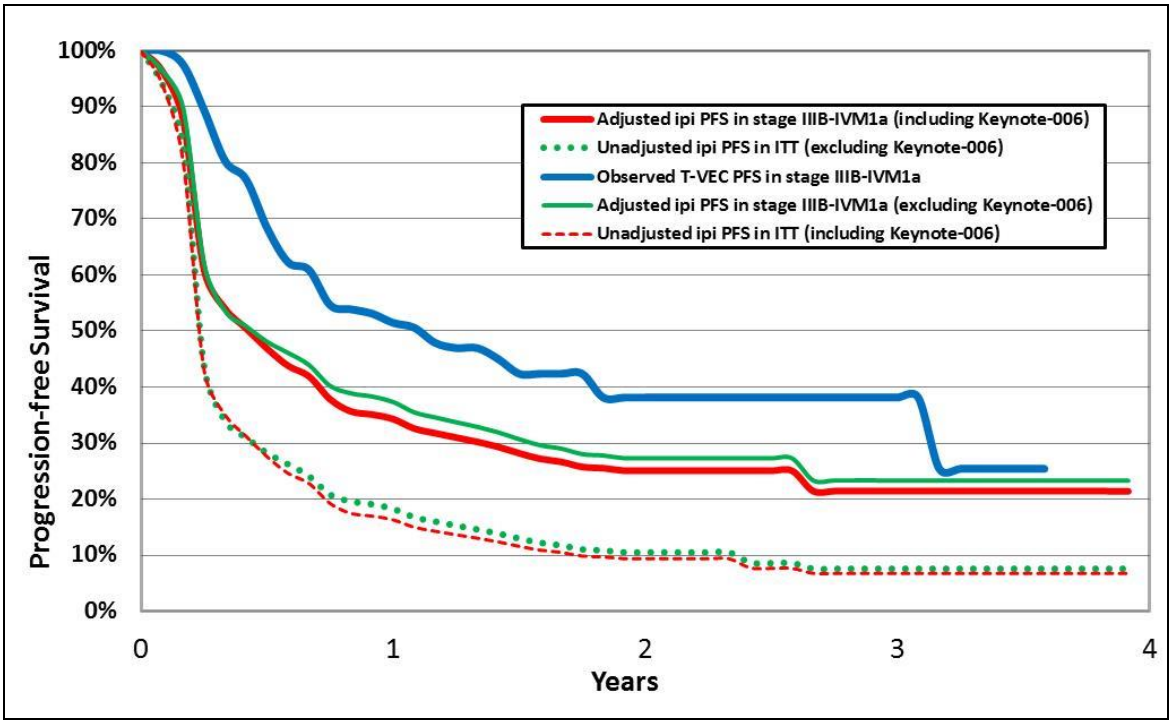


Figure 17 PFS curves including KEYNOTE 006 trial using modified Korn model

Ipi=ipilimumab; ITT=intent to treat; PFS=progression-free survival
Source: Response to the ERG's clarification letter, Figure A-5

Table 49 Median and mean PFS including or excluding KEYNOTE 006 using modified Korn model

Median or mean	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
Source: Response to ERG's clarification letter, Table A-9

11.3 Additional adverse events reported in the OPTiM trial

Table 50 summarises specific types of AEs reported in the OPTiM trial.[4] The most common treatment-related AEs associated with T-VEC are reported to be flu-like symptoms (fatigue, chills, pyrexia and "influenza-like illness"). Pruritis, injection-site erythema and injection site reaction were the only treatment-related AEs more common amongst patients treated with GM-CSF than with T-VEC in the licensed T-VEC population. Most of the AEs were also mild to moderate in severity. Grade 3 to 5 treatment-related AEs were uncommon in the T-VEC arm; in the licensed T-VEC population only fatigue and injection-site pain occurred at a frequency ≥1%. No Grade 3 or 5 treatment-related AEs were reported with GM-CSF.

Table 50 Summary of treatment-related AEs reported in the T-VEC licensed population of the OPTiM trial

Specific AE type	**Patients with each type of AE (%)**			
	T-VEC (n=163)		**GM-CSF (n=76)***	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Chills	49	0	4	0
Fatigue	45	2	32	0
Pyrexia	38	0	8	0
Influenza like illness	34	≤1	9	0
Injection-site pain	28	1	7	0
Nausea	25	≤1	12	0
Myalgia	17	≤1	5	0
Pain	15	≤1	9	0
Vomiting	13	≤1	5	0
Headache	13	≤1	8	0
Arthralgia	13	≤1	5	0
Diarrhoea	10	0	5	0
Pruritus	7	0	12	0
Injection-site erythema	6	0	20	0
Injection site reaction	4	0	12	0

AE=adverse event;
Source: CS, adapted from Table 4-34

The most common treatment-emergent SAEs (other than disease progression), as reported in the FDA briefing document[37] and draft EPAR[5] were cellulitis and pyrexia. These SAEs were reported in the overall safety population. Equivalent data were not reported in the CS for patients in the T-VEC licensed population.

The FDA briefing document[37] also highlights that six months after the last dose of therapy, preceded by three months of unsuccessful medical interventions a wound became resistant to medical therapy and required a below-the-knee amputation for a non-healing, infected wound in the left foot. Due to several confounders (e.g., treatment of the limb with radiation), the relationship of this event to T-VEC is however unclear. As this AE is not reported in the CS, it is also unclear whether this patient belonged to the T-VEC licensed population.

11.4 Non-RCT evidence

11.4.1 Trial characteristics of non-RCT evidence

The company presented evidence from one non-randomised single-arm multicentre Phase II study (Study 002/03;[39] NCT00289016) of T-VEC. This study was conducted in the UK and US and included 50 patients with stage IIIC to stage IV melanoma who were not eligible for curative surgery and who had one or more tumours accessible for direct injection.

Duration of follow-up was up was cited to be 47 weeks (CS, Table 4-28) but the median follow-up during the study was reported to be longer than this, 18 months (range, 11 to 36 months) (CS, page 99). Median duration in the study was reported to be 13.2 months (range 1 to 39 months) (CS, Table 4-30).

11.4.2 Patient characteristics of non-RCT evidence

In total, 23 patients had stage IIIC to stage IV M1a disease. Patient characteristics differed to the characteristics of patients enrolled in OPTiM trial:[4] the OPTiM trial[4] included proportionately more males, patients with ECOG PS 0, patients with elevated LDH levels and first-line patients than in the non-RCT. This study therefore appears to be less representative of patients likely to be considered for T-VEC in clinical practice than patients in the OPTiM trial.[4] The ERG therefore considers Study 002/03[39] to be of limited relevance to the company's decision problem

11.4.3 Assessment of methodological quality and risk of bias of non-RCT evidence

As noted in Section 4.1.1 (Table 3) the company did not use the most appropriate tool for assessing the methodological quality or risk of bias of Study 002/03.[39] Given the ERG considers that Study 002/03[39] is of limited relevance to the company's decision problem, the ERG has not conducted its own assessment.

11.4.4 Efficacy findings from non-RCT evidence

No results were reported for patients in the T-VEC licensed population. However, the following findings were reported for the overall study population:

- ORR was 26% (n=13); although not reported in the CS, this was highest for patients with stage IIIC disease (40%, n=4) as opposed to only 15% for patients with the most severe stage IV M1c disease
- Median OS was ≥ 16 months
- 1-year OS rate was 58%; although not reported in the CS, 1-year OS for patients with the most severe stage IV M1c disease was 40% (data not reported for stage III disease)
- 2-year OS rate was 52%.

11.4.5 Safety findings from non-RCT evidence

In total, 85% of patients had T-VEC related AEs. Six (12%) patients experienced pain that was potentially related to the underlying disease. There were 21 (42%) severe AEs, all of which were considered unrelated to T-VEC therapy. Fatigue/malaise (8%) and dyspnoea (8%) were the most common Grade 3 AEs; there were no Grade 4 or Grade 5 AEs.

11.4.6 Comparison of findings from non-RCT to findings from RCT

The ERG makes the following observations with regard to the findings from Study 002/03:[39]

- The ORR of 26% was similar to that observed in the ITT population in the OPTiM trial[4] (26%) but lower than in the T-VEC licensed population (41%)
- 1-year OS rate (58%) was lower than that estimated from the OPTiM trial[4] ITT population (74%) and T-VEC licensed population (87%)
- 2-year OS rate (52%) was similar to that estimated from the OPTiM trial[4] ITT population (50%) but lower than T-VEC licensed population (64%)
- Rates of specific AEs appeared to be higher in the non-RCT but this included only a small sample of patients.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report

Amgen Response: Factual inaccuracies

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Contains confidential information: AIC: Highlighted in yellow and underlined, CIC: Highlighted in turquoise and underlined

Issue 1 European Commission marketing authorisation status for talimogene laherparepvec

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1 page 9; Section 3.1 page 27. The report states that the a positive opinion for the granting of a marketing authorisation has been issued by the Committee for Medicinal Products for Human Use (CHMP) and is awaiting approval by the European Commission ([redacted])	Text should be updated to state that European Commission marketing authorisation for talimogene laherparepvec was granted on 16 December 2015	This update will remove any doubt regarding the final licensed population for talimogene laherparepvec. It should be noted that the final licensed population is the same as that recommended by the CHMP.	The ERG has made changes where appropriate to the report
Section 2.1, page 19; Section 8, page 100. The report states that T-VEC is 'expected to be licensed' and refers to the 'expected licensed population'.	Text should be updated to state that 'T-VEC is licensed' and to refer to 'the licensed population'	This update will remove any doubt regarding the final licensed population for talimogene laherparepvec. It should be noted that the final licensed population is the same as that recommended by the CHMP.	The ERG has made changes where appropriate to the report

Issue 2 OPTiM clinical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.5, page 44, Table 9 The % of patients discontinuing from treatment in OPTiM is incorrectly reported as 54.9 for T-VEC and 53.9 for GM-CSF in the ITT population	This should be corrected to 98.6% for T-VEC and 90.1% for GM-CSF as per Table 4-7 of the company submission	Data incorrect. If not amended, treatment discontinuation rates will appear too high and data will not be internally consistent within Table 9.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.2.6, page 46, Table 10 Table 10 title refers to 'final data cut', however DRR and ORR (per EAC) are presented from the primary data cut. These endpoints (per EAC) were only assessed at the primary data cut as specified in Table 6 of the report. Data could not subsequently change for these endpoints.	Remove 'final data cut' from the title of Table 10. Clarify within the table that DRR and ORR are presented at the primary data cut and that OS and TTF are presented at the final data cut.	For clarification purposes. There may be confusion when comparing Table 10 with Table 6 if not amended. Table 6 shows that DRR and ORR (per EAC) are only assessed at the primary data cut.	The ERG has amended table by amending the title and adding relevant footnotes The ERG has also amended the related text in the summary of the ERG report (page 10)
Section 4.2.6, page 46, Table 10 Table 10 has a column title of 'Patients with each type of AE (%)'.	Remove this column title	For clarification purposes. Column header is misleading as this table does not summarise AEs.	This column title was entered in error. The ERG has now removed this
Section 4.3.3, page 55 The report states that mean TTF is 'not reached'	The mean TTF should be corrected to 20.6 months as per Table 43 in the ERG report.	Data incorrect. If not amended, data will be inconsistent within the report.	The ERG agrees the mean value it cited in the text was incorrect. The ERG has amended text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4, page 56, Table 13 The incidence of all-cause treatment-emergent Grade 3 to 5 SAEs is reported as 'NR' in patients with non-visceral metastatic disease	This data can be derived (approximately) from company submission Table 4-32 by summing the percentages for Grade 3 to 5 AEs. 'NR' should be changed to '18%' for T-VEC and '10%' for GM-CSF.	Correction of data. Other data in Table 13 have been calculated by summing percentages from Table 4-32 in the company submission.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.4, page 56, Table 13 The following percentages that are quoted from the OPTiM CSR in the ITT population are incorrect - All cause treatment emergent Grade 3 to 5 AEs: [redacted]% T-VEC, [redacted] % GM-CSF - All cause treatment emergent Grade 3 to 5 SAEs: [redacted] % T-VEC	These percentages should be corrected as per Table 12-2 of the OPTiM CSR (14 April 2014): - All cause treatment emergent Grade 3 to 5 AEs: [redacted] % T-VEC, [redacted] % GM-CSF - All cause treatment emergent Grade 3 to 5 SAEs: [redacted] % T-VEC	Correction of data. Note that this has been marked up as AIC rather than CIC.	The ERG agrees the data it entered was incorrect. The ERG has amended data in table
Section 4.4, page 58, Table 15 Table 15 states that 9% of patients had 'treatment-related AEs leading to discontinuation'	This should be corrected to 'AEs leading to discontinuation'	Correction of data description as these are not specifically treatment-related AEs (see ERG report Table 13).	The ERG agrees the text it entered was incorrect. The ERG has amended text in table
Section 4.7, page 61 The report states the wrong number of patients in the OPTiM trial: 'a relatively large (n=463), open-label, multi-centre, international Phase III trial'.	The number of patients in the OPTiM trial should be corrected from n=463 to n=436	The number of patients is incorrectly stated for the pivotal registration trial. If not amended, patient numbers will be inconsistent within the report.	This was typographical error. The ERG has amended the text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7, page 61 The report states the wrong number of patients in the OPTiM licensed population: 'These findings were derived from an exploratory post-hoc analysis of 279 patients'	The number of patients in the OPTiM licensed population should be corrected from n=279 to n=249	The number of patients is incorrectly stated for the pivotal registration trial licensed population. If not amended, patient numbers will be inconsistent within the report.	This was typographical error. The ERG has amended the text

Issue 3 Talimogene laherparepvec license based on a post-hoc analysis of a subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 10; Section 1.3, page 12; Section 1.6.2, page 16; Section 4.2.6, page 47; Section 4.7, page 61; Section 8, page 100. The efficacy data in the licensed population (stage IIIB - IVM1a) is described as coming from a post-hoc subgroup analysis of OPTiM (where post-hoc analysis refers to those in which the hypotheses being tested are not specified before any examination of the data).	We propose that the wording 'post-hoc' should be clarified by noting that subgroup analysis by disease stage (IIIB/C, IVM1a, IVM1b, IVM1c) was not post-hoc. It is the specific grouping of stage IIIB-IVM1a disease that was not prespecified.	The wording 'post hoc' is somewhat misleading since subgroup analysis by disease stage was prespecified in the OPTiM statistical analysis plan (as acknowledged in Table 7 of the ERG report). Disease stage was also a randomisation stratification factor (IIIB/C vs IVM1a vs IVM1b vs IVM1c). The credibility of the disease stage subgroup analyses was fully discussed with the EMA and the draft EPAR acknowledges that these analyses adhered to the EMA guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). The draft EPAR confirms that 'robust statistical analyses based on pre-specification of covariate, replication across studies (study 005/05 and 002/03), consistency across endpoints, statistical significance of treatment-by-covariate interaction and biological plausibility of the observed effect' were performed. These subgroup analyses showed that efficacy was most pronounced in stage IIIB-IVM1a patients which led to the licensed indication.	The ERG agrees that the following subgroups were pre-specified by disease stage: • IIIB/C • IV M1a • IV M1b • IV M1c However the subgroup of patients with stage IIIB to stage IV M1a disease were not a pre-defined subgroup and therefore analysis of this subgroup of patients constitutes a post-hoc analysis. The text has been altered for greater clarity in 2 places: • Section 1.2, page 10 • Section 4.2.6, page 47

Issue 4 OS data used in the OPTiM economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, page 15; Section 5.5.2, page 90 The report incorrectly states that OS data from the earlier, less mature data cut of OPTiM were used in the company model, as opposed to data from the final data cut.	The report should make clear that OS data from the OPTiM final data cut were used in the company model.	Correction of stated data used in the model.	The ERG has deleted reference to the OS being from an earlier data cut

Issue 5 Generalisability of OPTiM licensed population to clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, page 12 The report refers to stage IIIC-IVM1a rather than stage IIIB-IVM1a as the expected patient population for T-VEC in clinical practice: 'Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with stage IIIC to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England'	Sentence should be amended to 'Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with stage IIIB to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England'	Correction of expected patient population.	This was typographical error. The ERG has amended the text

STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/04

Erratum completed 5th February 2016

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 5 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. All were considered by the ERG to require minor changes to the text. The pages of the report affected are presented here. Please note:

- New text added by the ERG is in italics and underlined.
- Text deleted completely (as opposed to being re-worded) is struck out.
- Unaltered text which is considered to be of relevant context to that added, amended or deleted (such as headings or sentences preceding or following the added, amended or deleted text) is presented in its original font.
- All other unaltered text is greyed out.

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Amgen Limited in support of the use of talimogene laherparepvec (Imlygic®) (hereafter referred to as T-VEC) to treat patients with non-visceral metastatic melanoma.

1.1 Critique of the decision problem in the company's submission

The intervention specified in the NICE scope is T-VEC. It has been recognised by the European Medicines Agency (EMA) as a novel, first-in-class oncolytic immunotherapy treatment. *A marketing authorisation was granted from the European Commission on 16 December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease.* The company estimates that, if recommended by NICE, 728 patients in England would be eligible for treatment with T-VEC in 2015.

The population specified in the NICE scope is adults with stage IIIB to stage IV melanoma. *This is the same patient population for which T-VEC is licensed.* However, as T-VEC is administered by intralesional injection, its use will be restricted to patients whose melanoma is considered injectable, i.e. there must be cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance.

The following comparators are specified in the NICE scope: ipilimumab, vemurafenib and dabrafenib. Unfortunately, none of these drugs has been studied in trials comprising only patients with non-visceral metastatic stage IIIB to stage IV M1a melanoma or in trials where these patients are a specified subgroup. Ipilimumab is considered by the company to be the primary comparator to T-VEC and vemurafenib and dabrafenib are not evaluated in the company submission (CS). However, with NICE's recent recommendation that pembrolizumab should be made available through the NHS as a treatment for some patients with metastatic melanoma, the ERG considers that, in future, all patients who are currently offered first- or second-line treatment with ipilimumab will now be offered pembrolizumab (if they have not already received it).

Clinical evidence is reported in the CS for all five outcomes specified in the NICE scope: overall survival (OS), progression-free survival (PFS), tumour response rate, adverse events (AEs) of treatment and health-related quality of life (HRQoL). These are all outcomes that

are commonly measured in metastatic melanoma drug trials. In addition, durable response rate (DRR) was also reported as the primary outcome in the OPTiM trial from which the majority of evidence for T-VEC is derived; DRR is a non-validated, albeit a clinically relevant, endpoint. The OPTiM trial reported time to treatment failure (TTF) instead of PFS since patients were permitted to continue to receive treatment despite showing evidence of disease progression with T-VEC.

1.2 Summary of clinical effectiveness evidence submitted by the company

Evidence for the relative efficacy of T-VEC was obtained from the OPTiM randomised controlled trial (RCT). Evidence from one Phase II non-RCT (Study 002/03) is also presented in the CS.

In the open label OPTiM trial patients with stage IIIB to stage IV M1c disease were randomised in a 2:1 ratio to receive either T-VEC (n=295) or granulocyte macrophage colony-stimulating factor (GM-CSF) (n=141). *The licence* for T-VEC is based on clinical data from a subgroup of these patients (n=249), namely patients with injectable non-visceral metastatic melanoma (i.e. stage IIIB to stage IV M1a disease); *although subgroup analyses by different stages of disease (stage IIIB to IIIC, stage IV M1a, stage IV M1b and stage IV M1c) were all pre-specified, stage IIIB to stage IV M1a disease was not a pre-specified subgroup but rather defined post-hoc.* Post-hoc analysis refers to those in which the hypotheses being tested are not specified before any examination of the data. *The results for analyses for this subgroup are:*

- DRR by Endpoint Assessment Committee (EAC) *(primary data cut)* assessment was higher in patients treated with T-VEC compared with GM-CSF (25.2% vs 1.2%; unadjusted odds ratio 28.6; [95% CI: 3.9 to 211.5]; p<0.0001)
- TTF by investigator assessment *(final data cut)* was longer in the T-VEC arm than in the GM-CSF arm (median 13.1 months vs 3.3 months; hazard ratio [HR]=0.28; [95% CI: 0.20 to 0.40]; p<0.0001)
- Overall tumour response rate by EAC assessment *(primary data cut)* was higher in the T-VEC arm than in the GM-CSF arm (40.5% vs 2.3%, p<0.0001)
- At the final OS analysis *(final data cut),* median OS gain was 25.3 months for patients in the T-VEC arm vs patients in the GM-CSF arm (median 46.8 months vs 21.5 months, unstratified HR=0.56; [95% CI: 0.40 to 0.79]; p=0.0008).

In patients with non-visceral metastatic disease treated with T-VEC, treatment-related Grade 3 to 5 AEs and treatment-related serious AEs (SAEs) were reported by 14% and 6% of patients respectively, and treatment emergent AEs leading to discontinuation were reported by 9% of patients. In the overall trial population, the most common AEs reported by patients receiving T-VEC were flu-like symptoms (90%) and injection-site reactions (42%)..

Overall, the ERG considers that patients with non-visceral metastatic disease in the OPTiM trial are generally similar to the patients with *stage IIIB* to stage IV M1a disease likely to be considered for treatment with T-VEC in clinical practice in England.

The ERG has concerns that the population considered in this STA is one that has been constructed following the results of a post-hoc analysis of data collected during the OPTiM trial. The ERG is particularly concerned that the *differential survival trajectory* of patients with stage III disease is likely to differ from that of those with stage IV M1a disease. Furthermore, the ERG considers that the OPTiM trial may be subject to bias due to limited blinding, a higher proportion of dropouts in the GM-CSF arm (particularly in the first few months of the trial), and the use of DRR as the primary endpoint. It is noted in the draft European Public Assessment Report (EPAR) that DRR is a new, clinically relevant, endpoint that is non-validated and is potentially prone to bias. However, the ERG does not consider that the potential sources of bias fully explain the improvements in efficacy in the T-VEC arm compared with the GM-CSF arm. The ERG notes that a further uncertainty, raised by the US Food and Drug Administration (FDA), relates to the size of lesions. The results of an FDA post-hoc analysis of the overall intention-to-treat population (i.e. including those with stage IV M1b and stage IV M1c disease) suggest that patients who had very small lesions (<1 cm^2) were more likely to respond to T-VEC than were the overall population (10.1%). The ERG further notes that evidence for the effectiveness of T-VEC treatment is not presented by line of therapy in the subgroup of patients with non-visceral metastatic disease.

Results from the OPTiM trial suggest that T-VEC's safety profile compares favourably with those of the comparator treatments detailed in the NICE scope. The ERG, however, notes that there are limited data to support the long-term safety of treatment with T-VEC.

Although HRQoL data collected as part of the OPTiM trial show that, in general, quality of life for patients receiving T-VEC was better than for those receiving GM-CSF, a substantial proportion of patients in the GM-CSF arm did not complete HRQoL assessments, suggesting that the HRQoL findings should be interpreted with caution.

For reasons highlighted in Section 1.5, the ERG does not consider the ipilimumab survival estimates generated by the company, using either the modified Korn model or the two-step Korn model to be reliable. It is, therefore, impossible to determine the relative clinical effectiveness of T-VEC compared with any of the comparators listed in the NICE scope.

using data from patients with predominantly stage IV M1b and stage IV M1c disease, whilst it is patients with stage IV M1a disease who mostly feature in the OPTiM trial. Furthermore, in the OPTiM trial 54.7% of T-VEC patients had stage IIIB, stage IIIC or stage IV M1a disease compared with less than 20% in the ipilimumab trials

3. There is no information in the public domain relating to the way in which the original (published) Korn model has been modified or to the data used to calibrate the model. It is likely that the issues outlined in point 2 also hold for the modified Korn model. In addition, the modified Korn model includes an adjustment for elevated lactate dehydrogenase (LDH), which is not relevant for patients with stage IIIB, stage IIIC or stage IV M1a disease, but has the effect of reducing the size of the coefficients associated with other adjustment factors (and improving the relative efficacy of T-VEC)
4. The effectiveness of ipilimumab may vary significantly by stage of disease. The company has attempted to correct for this case-mix imbalance by using the two-step Korn model, which is a further application of the modified Korn model. This additional adjustment is likely to mean that the problems previously described are further compounded
5. The original Korn publication includes both PFS and OS models. The PFS model is quite different from the OS model. The ERG, therefore, concludes that the company's use of the same modified Korn model for both OS and PFS is inappropriate.

Within the company model, different methods are applied sequentially to estimate OS. A number of issues with this approach were identified by the ERG, including:

1. ~~OS data from the earlier, less mature, data cut of the OPTiM trial were used by the company~~
2. The exponential trend used by the company to project OS for patients treated with T-VEC deviates markedly from the final recorded OPTiM trial data
3. For patients with stage I, stage II and stage III disease, the American Joint Committee on Cancer (AJCC) survival trends provide results from the date of diagnosis, whilst for patients with stage IV disease trends are recorded from the time of identification of first distant metastases. The relevance of these mixed AJCC adjusted mortality estimates is highly questionable
4. The data on which the AJCC analyses were performed were gathered prior to the current era of novel immunological treatments and may be unrealistic as these newer treatments have significantly altered the prospects for many patients
5. A sudden increase in the mortality rate after 270 weeks (62.1 months) is observed in the company model. The ERG considers that this effect is arbitrary and without any clinical justification
6. After 10 years, UK life table mortality rates are applied within the company model without adjustment, other than for age and sex. This implies that the cohort of long-term survivors is suddenly cured at this time point.

Other model-related issues identified by the ERG include an error in the discounting calculation, poor choice of health state utility values, lack of use of a terminal state disutility, use of a half-cycle (rather than a mid-cycle) continuity correction and a PSA ICER calculation error.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical evidence

- Results from the OPTiM trial show that the effectiveness of T-VEC is markedly improved in the subgroup of patients with stage IIIB to stage IV M1a disease when compared with the overall trial population (which includes patients with stage IV M1b and M1c disease)
- Evidence from the OPTiM trial suggests that the safety profile of T-VEC compares favourably to the safety profile of the comparators listed in the NICE scope
- The company has made thorough attempts to identify studies that include both a relevant treatment comparator to T-VEC and a relevant patient population.

Cost effectiveness evidence

- The company supported the appraisal process by providing the additional analyses requested by the ERG in a timely manner.

1.6.2 Weaknesses and areas of uncertainty

Clinical evidence

- Following the very recent approval of pembrolizumab for the first- and second-line treatment of patients with metastatic malignant melanoma, clinicians' first choice of systemic treatment for this population is likely to shift away from ipilimumab towards pembrolizumab
- The efficacy data *for the T-VEC licensed population* (patients with non-visceral metastatic melanoma) has been extracted from a post-hoc subgroup data analysis from the OPTiM trial
- The OPTiM trial may be subject to bias due to limited blinding and a higher proportion of dropouts in the GM-CSF arm (particularly in the first few months of the trial)
- The use of DRR as the primary endpoint in the OPTiM trial raises concerns as DRR is a new, albeit clinically relevant, endpoint which is non-validated and is potentially prone to bias
- The results of an FDA post-hoc analysis suggest that patients who had very small lesions (<1 cm^2) were more likely to respond to T-VEC than the overall population
- Two areas where evidence relating to treatment with T-VEC is lacking are in relation to line of treatment and long-term safety
- The relative clinical effectiveness of T-VEC compared with any treatment currently used in clinical practice is unknown.

Cost effectiveness evidence

- The ERG does not consider that the synthesised ipilimumab comparator is sufficiently reliable to support a valid assessment of the cost effectiveness of treatment with T-VEC vs ipilimumab

3.1 Population

The population specified in the NICE scope is adults with stage IIIB to stage IV melanoma. *A marketing authorisation was granted from the European Commission on 16 December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease.* These patients with non-visceral metastatic melanoma are referenced in the company's description of the population in the decision problem. Therefore, the clinical evidence presented by the company is only applicable to a subgroup of the patients specified in the NICE scope.

Importantly, but not explicitly stated in either the NICE scope or company's decision problem or in *the licence,* as T-VEC is administered by intralesional injection, the patient population is further restricted to patient's whose melanoma is considered injectable, i.e. there must be cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance. Patient experience of injectable treatments is not discussed in the CS. The ERG is not confident that all patients with injectable melanoma will be accepting of this type of treatment every 2 weeks over a long period of time.

Just under three-quarters (73%) of patients with metastatic non-visceral disease are considered by the company to have injectable disease. The population in the OPTiM trial[4] is therefore not directly comparable with patients in other trials for two reasons: (i) as noted by the ERG in Section 2.2 (Table 1), no other trial has conducted a subgroup analysis of patients with stage IIIB to stage IV M1a disease and (ii) only the OPTiM trial[4] has included patients solely with injectable disease.

3.2 Intervention

The intervention specified in the CS and in the company's decision problem statement is an oncolytic virus, T-VEC, derived from the herpes simplex virus type-1 (HSV-1) that has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein granulocyte-macrophage colony-stimulating factor (GM-CSF). The aim of treatment is to boost the body's immune system to protect itself from carcinogenesis and progression of cancer.[34,35]

T-VEC has two complementary mechanisms of action in/on cancerous cells:[36] (i) replication that causes cell rupture/lysis and death (intracellular or direct effect) (ii) post-lysis release of tumour-derived antigens and GM-CSF, stimulating a systemic immune response from antigen-presenting cells (APCs) upon distant tumour sites (extracellular or indirect effect).

A summary of the reasons for discontinuing treatment and the reasons for discontinuing to participate in the trial is presented in Table 9.

Table 9 Summary of the reasons for discontinuing treatment and the reasons for discontinuing to participate in the OPTiM trial (primary analysis)

Reason for discontinuing treatment and from study	stage IIIB–stage IV M1a (T-VEC licensed population)		stage IIIB to stage IV M1c (ITT population)	
	T-VEC (n=163)	GM-CSF (n=86)	T-VEC (n=295)	GM-CSF (n=141)
Not treated (%)	[redacted]	[redacted]	1.4	9.9
Discontinued from treatment (%)	[redacted]	[redacted]	*98.6*	*90.1*
• Maximum allowed dose without PR/CR	[redacted]	[redacted]	8.8	6.4
• PR or CR for at least 6 continuous months	[redacted]	[redacted]	14.2	0
• Progressive disease	[redacted]	[redacted]	64.7	67.4
• Adverse event	[redacted]	[redacted]	3.7	2.1
• Deaths	[redacted]	[redacted]	1.7	2.1
• Consent withdrawn	[redacted]	[redacted]	3.4	8.5
• Physician decision	[redacted]	[redacted]	2.0	3.5
Discontinued from trial after receiving treatment (%)	[redacted]	[redacted]	56.9	70.2
• Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]
• Deaths	[redacted]	[redacted]	[redacted]	[redacted]
• Consent withdrawn	[redacted]	[redacted]	[redacted]	[redacted]
• Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
• Other	[redacted]	[redacted]	[redacted]	[redacted]

CR=complete response; PR=partial response

Source: CS, adapted from Figure 4-4 and Table 4-7, CSR (Primary Analysis), adapted from *Table 14-1.1* and company's response to clarification letter, adapted from Table A-13 and Figure A-6

Importantly, the EMA has noted that early treatment discontinuation in the GM-CSF arm could have potentially disproportionately affected the OS results in favour of T-VEC.5 However, the EMA also states that a sensitivity analysis submitted by the company clarified that the patients who discontinued early did not affect the observed treatment difference in the ITT population for OS (draft EPAR,5 Table 32) or DRR (draft EPAR,5 Table 37).

The EMA has also highlighted that there was a higher proportion of patients with major protocol deviations in the T-VEC arm (12.2%) than in the GM-CSF arm (3.5%).5 Missing confirmatory scans were reported to be the most common protocol deviation (6.1% vs 0.7%,

4.2.6 Results from OPTiM trial

All pre-specified primary, secondary and tertiary efficacy outcomes from the OPTiM trial[4] have been reported by the company. The key results are summarised in Table 10. In both the ITT population and subgroup of patients with non-visceral disease, T-VEC is significantly more efficacious than GM-CSF for all key outcomes.

Table 10 Summary of key efficacy results in the OPTiM trial ~~(final data cut)~~

Outcome	~~Patients with each type of AE (%)~~			
	Patients with non-visceral metastatic disease		ITT population	
	T-VEC (n=163)	GM-CSF (n=86)	T-VEC (n=295)	GM-CSF (n=141)
DRR by EAC assessment (%)*	25.2	1.2	16.3	2.1
Unadjusted odds ratio (95% confidence interval)	28.6 (3.9 to 211.5)		8.9 (2.7 to 29.2)	
P-value	<0.0001		<0.0001	
ORR by EAC assessment (%)*	40.5	2.3	26.4	5.7
P-value	<0.0001		<0.0001	
Median TTF by investigator assessment (months)†	13.1	3.3	8.1	2.9
Hazard ratio (95% confidence interval)	0.28 (0.20 to 0.40)		0.43 (0.33 to 0.56)	
P-value	<0.0001		<0.0001	
Median OS (months)†	46.8	21.5	23.3	18.9
Hazard ratio (95% confidence interval)	0.56 (0.40 to 0.79)		0.79 (0.62 to 1.00)	
P-value	0.0008		0.0494	

DRR=duration of response rate; ITT=intention to treat; OS=overall survival; TTF=time to treatment failure
**Primary data-cut*
†Final data-cut
Source: CS, adapted from Table 4-13, Table 4-16, Table 4-14 and clarification response, Table A-12 (patients with non-visceral metastatic disease) and appendices to CS, adapted from Table 1-13, Table 1-15, Table 1-17 and Table 1-14 (ITT population)

Subgroup analyses of ITT population

Subgroup analyses for DRR and OS suggested that the treatment effect of T-VEC may differ according to disease stage, prior non-surgical melanoma treatment, line of therapy, presence of visceral disease, and (for DRR only) by geographic region. The p-values for the tests for interaction for these subgroup analyses are provided in appendices to this ERG report (Section 11.1).

In an exploratory post-hoc analysis of data for patients in the ITT population which was presented in the FDA briefing document,[37] a larger proportion (30.4%) of patients with a DR had only very small lesions (<1cm^2) compared to the overall population (10.1%). The FDA interpreted this to suggest that patients who had larger lesions were less likely to respond to T-VEC, although it also cautioned that the clinical meaningfulness of a response (and therefore DRR) is questioned for patients with already relatively small baseline lesions.

Subgroup of patients with non-visceral metastatic disease

In the subgroup of patients with non-visceral metastatic disease, it was noticeable that the CR rate was higher in the T-VEC arm than in the GM-CSF arm (16.6% vs 0.0%; $p < 0.001$; primary data cut). Furthermore, results of an analysis presented in the draft EPAR5 show that in patients with non-visceral metastatic disease, patients receiving ≥ second-line T-VEC also had improved DRR (17% vs 2%) and objective response (28% vs 2%) relative to GM-CSF. However the p-values for the tests for interaction for these subgroup analyses were not provided.

After treatment failure, a greater proportion of patients in the GM-CSF arm received subsequent ipilimumab, vemurafenib, dabrafenib, trametinib or an anti-PD1 antibody (such as pembrolizumab) than patients in the T-VEC arm (50% and 41% respectively in T-VEC licensed population). Ipilimumab was the most common subsequent treatment (37% of patients in both arms). Vemurafenib and anti-PD1 antibodies (such as pembrolizumab) were both more commonly given to patients who failed treatment with GM-CSF than T-VEC: 15% vs 9% (vemurafenib) and 5% vs 1% (anti-PD1 antibodies) respectively.

The annual survival rates for patients in the T-VEC licensed population were consistently higher in the T-VEC treatment group compared with the GM-CSF arm. After 3 years, the survival rate for patients in the T-VEC treatment group was 54.9% compared with a survival rate of 34.6% for patients in the GM-CSF treatment group. Moreover, the survival rate in the T-VEC arm appeared to be stable over 4 and 5 years, and the difference in long-term survival rates at 4-years between T-VEC patients and GM-CSF patients was more than 20% (48.9% vs 27.5%).

Summary of findings and ERG comment

The company states that the results from patients with non-visceral metastatic disease are in line with the results from the ITT population. The ERG notes that the magnitude of difference between arms for all endpoints is much greater in patients with non-visceral metastatic disease than in the ITT population. Given the potential risks of bias identified in Section 4.2.5, the ERG cautions that it is difficult to argue that there is a demonstrable OS benefit for T-VEC over GM-CSF in the ITT population. On the other hand, in patients with non-visceral metastatic disease, there does seem to be a demonstrable benefit; the difference in efficacy endpoints between arms is large and is unlikely to be explained by methodological bias.

Although subgroup analyses by different stages of disease (stage IIIB to IIIC, stage IV M1a, stage IV M1b and stage IV M1c) were all pre-specified, the definition of non-visceral disease used by the company (stage IIIB to stage IV M1a disease) was not a pre-specified subgroup

but rather defined post-hoc. Hence the findings for patients with non-visceral metastatic disease are derived solely from an analysis of an exploratory post-hoc subgroup. Carrying out such analyses risks identifying subgroups in which superior drug efficacy occurs only by chance. However, the ERG's primary concern is that the subgroup comprises a mixture of patients with stage III and patients with stage IV disease. This is an issue as the *differential survival trajectory* for patients with stage III disease is likely to differ from that of patients with stage IV disease.

The company did not attempt to employ the modified Korn model or the two-step Korn model to adjust the survival curves of patients receiving BRAF inhibitors. The reason given for this was that the trials included in the meta-analysis which forms the basis for the original Korn[51] model did not differentiate patients by BRAF status. The ERG concurs with the company.

The results of the two-step Korn model are more conservative than the results from implementing the modified Korn model as the two-step approach assumes that ipilimumab is more effective in patients with non-visceral metastatic melanoma than in the wider population of patients with metastatic melanoma (predominantly later stage disease). Hence, the latter is considered to generate "best case" findings and the former "worst case" findings. More information about the Korn models is presented in the appendices to this ERG report (Section 11.2).

In summary, the trial results for T-VEC are: median OS: 46.8 months; mean OS: 36.9 months; median TTF: 13.1 months; *mean TTF: 20.6 months*; TTF is considered by the company to be a proxy for PFS. For ipilimumab, the adjusted results, as presented in the company's response to the ERG's clarification letter, are:

- Modified Korn model results for ipilimumab:
  - median OS increases from 10.9 months to 21.3 months (95% prediction interval: 14.6 months to upper interval not reached)
  - mean OS increases from 19.5 to 29.2 months (95% prediction interval: 23.8 months to 34.6 months)
  - median PFS increases from 2.8 months to 5.3 months
  - mean PFS increases from 8.0 to 15.2 months.
- Two-step Korn model results for ipilimumab:
  - median OS increases from 10.9 months to median not reached (95% prediction interval: 27.0 months to upper interval not reached)
  - mean OS increases from 18.0 to 32.3 months (95% prediction interval: 28.1 months to 35.8 months)
  - median PFS increases from 2.8 months to 17.6 months
  - mean PFS increases from 7.4 to 18.6 months.

Given the lack of clinical effectiveness evidence available, the ERG considers that the company was correct to attempt to apply alternative approaches for the comparison of T-VEC with ipilimumab. However, for reasons described in Section 5.5.1 the ERG does not consider that the use of either of the Korn models was appropriate. Therefore, the ERG does not consider the findings reported by the company when utilising the modified Korn model or the two-step Korn model to be either reliable or robust.

4.4 Safety

AE data are available for patients treated with T-VEC; these data have been previously reported for the OPTiM trial overall safety population (patients with stage IIB to stage IV M1c disease) in the published paper[4] and in the draft EPAR.[5] In the CS, the company reports only AEs for patients with non-visceral metastatic disease. Data for both populations are summarised by the ERG in Table 13 and a summary of the specific types of AEs and serious AEs (SAEs) is presented in the appendices of the ERG report (Section 11.3, Table 50).

Table 13 Summary of safety profiles of T-VEC and GM-CSF in the OPTiM trial

Type of safety concern	Patients with each type of AE (%)			
	Patients with non-visceral metastatic disease		Overall safety population*	
	T-VEC (n=163)	GM-CSF (n=76)	T-VEC (n=292)	GM-CSF (n=127)
All cause and any Grade treatment emergent AE	99	93	99	95
All cause treatment emergent Grade 3 to 5 AEs	33	23	[redacted]†	[redacted]†
All cause and any Grade treatment emergent SAE	20	13	26	13
All cause treatment emergent Grade 3 to 5 SAEs	*18*	*10*	[redacted]†	[redacted]†
Treatment-related AEs	93	79	93	80
Treatment-related Grade 3 to 5 AEs	14	5	[redacted]†	[redacted]†
Treatment-related SAE	6	0	7	0
Treatment emergent AE leading to discontinuation	9	7	10	6
Fatal AEs on study	1	0	3	2

AE=adverse event; NR=not reported; SAE=serious adverse event
Source: CS, adapted from Table 4-32 and *draft EPAR,[5] Table 46 except † taken from CSR, Table 12-2

The ERG concurs with the company that treatment emergent AEs, SAEs and treatment-related AEs were higher in the T-VEC arm than in the GM-CSF arm. In patients with non-visceral metastatic disease, AEs leading to treatment discontinuation were reported to be similar between arms and there was only one fatal AE, in the T-VEC arm, but this was not related to treatment. The ERG notes that treatment discontinuation rates due to AEs were marginally higher in the T-VEC arm than in the GM-CSF arm in the overall safety population.

Adverse events of special interest (AEOSIs) have also been identified by the company, and feature in the risk management plan (RMP), agreed with the EMA,[5] as being important safety concerns. These AEOSIs were not fully reported in the CS. The ERG has summarised the AEOSI data in Table 14; these events include flu-like symptoms, injection site reactions and cellulitis. The draft EPAR[5] states that the majority (70% to 90%) of the flu-like symptoms were reported to resolve within 72 hours. These events were also reported more frequently within the period of the first six treatments, particularly in patients who were HSV-1 negative at baseline, due to the intratumoral injection route of administration of T-

Table 15 Adverse events reported during pivotal trials with ipilimumab, vemurafenib, dabrafenib, pembrolizumab and T-VEC

Trial/ treatment	Frequency of any treatment emergent and/or treatment-related AEs, dose discontinuations and/or modifications due to AEs (%)		Common AEs	
MDX010-20[19]/ Ipilimumab (Previously treated)	Grade 3 or 4 treatment-related AEs	23	AEs were mostly immune-related which may involve the gastrointestinal, liver, skin, nervous, endocrine, ocular, or other organ systems	
	Treatment-related AEs leading to discontinuation	10		
BRIM-3[17]/ Vemurafenib (First-line)	Grade 3 to 5 AEs	50	Most frequently occurring Grade 3 or 4 AEs (%):	
	SAEs	33		
	AEs leading to treatment discontinuation	7	Cutaneous SCC	19
	AEs leading to dose modification/ interruption	38	Increase in LFT	11
			Keratoacanthoma	10
			Rash	9
			Arthralgia	6
BREAK-3[18]/ DTIC (First-line)	Grade 3 to 5 AEs	42	Most frequently occurring Grade 3 to 5 AEs (%):	
	SAEs	23		
	Treatment-related SAEs	15	Back pain	4
	AEs leading to treatment discontinuation	3	Hyperglycaemia	3
	AEs leading to dose reduction	18	Pyrexia	3
	AEs leading to dose interruption	27	GGT increased	3
KEYNOTE-006[21]/ Pembrolizumab (First-line)	Grade 3 to 5 AEs	35	Most frequently occurring Grade 3 to 5 AEOSIs (%):	
	Grade 3 to 5 treatment-related AEs	12		
	SAEs	25	Colitis	3
	Treatment-related SAEs	9	Hepatitis	2
	Treatment-related AEs leading to discontinuation	9	Diarrhoea	1
KEYNOTE-006[21]/ Ipiliumumab (First-line)	Grade 3 to 5 AEs	37	Most frequently occurring Grade 3 to 5 AEOSIs (%):	
	Grade 3 to 5 treatment-related AEs	20		
	SAEs	30	Colitis	7
	Treatment-related SAEs	18	Diarrhoea	4
	Treatment-related AEs leading to discontinuation	9	Hypophysitis	2
OPTiM trial[4]*/ T-VEC (Previously treated and untreated)	Grade 3 to 5 AEs	33	Most frequently occurring Grade 3 to 5 AEs (%):	
	Grade 3 to 5 treatment-related AEs	14		
	SAEs	20	Fatigue	2
	Treatment-related SAEs	6	Injection-site pain	1
	AEs leading to discontinuation	9		

AE=adverse event; AEOSI=adverse event of special interest; CS=company submission; GGT= Gamma-glutamyl transferase; LFT=liver function tests; SCC=squamous-cell carcinoma

*T-VEC licensed population only

Source: CS, adapted from Table 4-38 and text of pages 198 to 109 with additional data reported for BRIM-3[17] and BREAK-3[18] taken from ERG report submitted during the dabrafenib STA[53] and from the company's submission (Merck) for pembrolizumab for previously untreated ipilimumab naïve patients[54]

4.7 Conclusions of the clinical effectiveness section

The majority of evidence for the clinical effectiveness of T-VEC is derived from the OPTiM trial,[4] a relatively large (*n=436*), open-label, multi-centre, international Phase III trial which included patients from the UK (n=33 [8%]). ITT population (patients with stage IIIB to stage IV M1c disease) results show statistically significant improvements in favour of T-VEC vs GM-CSF for DRR, TTF (a proxy for PFS in this trial) and ORR but not for OS (although the OS gain was close to being statistically significant).

Findings from the OPTiM trial[4] were reported for patients with non-visceral metastatic melanoma (patients with stage IIIB to stage IV M1a disease); these patients are the focus of this appraisal as these are the patients for whom T-VEC will be licensed. Statistically significant improvements in DRR, TTF, ORR and OS were reported for patients treated with T-VEC compared with those treated with GM-CSF. The magnitude of the effect in the licensed population is much greater for all outcomes than in the ITT population. These findings were derived from an exploratory post-hoc analysis of *249* patients.

The ERG has concerns that the population considered in this STA comprises a mixture of patients with stage III and stage IV M1a disease as it is likely that the *differential survival trajectory* of patients with stage III disease differs from that of patients with stage IV disease. The ERG also considers that there are a number of potentially important sources of bias in the OPTiM trial[4] due to limited blinding, a higher proportion of drop-outs in the GM-CSF arm (particularly in the first few months of the trial), and the use of DRR as the primary endpoint. However, the ERG does not consider that the potential sources of bias explain the improvements in efficacy in the T-VEC arm compared with the GM-CSF arm reported for patients with non-visceral disease.

An area of uncertainty that has been raised by the FDA[37] relates to the size of lesions. The results of an FDA post-hoc analysis suggest that patients who had very small lesions (<1cm^2) were more likely to respond to T-VEC than the overall population (30.4% vs 10.1% respectively).[37]

In both the overall trial population and the subgroup of patients with non-visceral metastatic melanoma, there were more treatment emergent AEs, SAEs and treatment-related AEs in the T-VEC arm of the OPTiM trial[4] than in the GM-CSF arm. The types of AEs included flu-like symptoms (very common), injection site reactions (very common) and cellulitis (common and potentially serious). Careful wound care is important to minimise risk of infection, particularly if tissue necrosis results in open wounds. In terms of the types of AEs observed, T-VEC compares favourably in terms of safety to other recommended treatments

5.4 ERG's critique of the submitted economic evaluation

5.4.1 NICE reference case checklist

Table 33 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. The economic evaluation considers a subgroup of that issued in the final NICE scope in line with *the marketing authorisation for T-VEC.* The decision problem addressed in the submission is adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease (disease stage IIIB–stage IV M1a)
Comparator(s)	As listed in the scope developed by NICE	Partial. The company considers that BRAF inhibitors are unlikely to be treatment options for the stage IIIB to stage IV M1a population and that ipilimumab is the primary comparator
Perspective on costs	NHS and PSS	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Patient related direct health effects are considered. No impact on carers has been considered in the model
Form of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 30 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	No – no connected evidence network is possible. A synthesised comparator was developed from three arms of two ipilimumab trials with adjustments to match baseline patient characteristics
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs, using utility estimates from other NICE appraisals which used the EQ-5D instrument
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes, HRQoL data were collected as part of the OPTiM trial[4] but these were not suitable for utility estimation
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes, partially - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model

EQ-5D=EuroQol-5 dimension; PPS=personal social services; QALY=quality adjusted life year

It is generally appropriate to use K-M analysis results directly in a model prior to use of projection methods. ~~However, in this case, it appears that the final analysis of the trial data (CS, Figure 4-6) has not been used in the model, which includes only OS data from the earlier, less mature, data cut.~~ The ERG has carried out a curve-fitting exercise to a re-analysis of the final data cut which was requested during the clarification process. The ERG has found that a 2-part exponential model (Figure 9) closely follows the trial OS data from 9 months until the last recorded death (47 months).

It is noteworthy that the company model exponential trend (Phase 1b in Figure 8) deviates markedly from the final recorded trial data and leads to a clear separation from the exponential trend identified by the ERG. This results in a much more advantageous OS estimate for T-VEC compared to the long-term projection resulting from the fitted ERG curve (Figure 9).

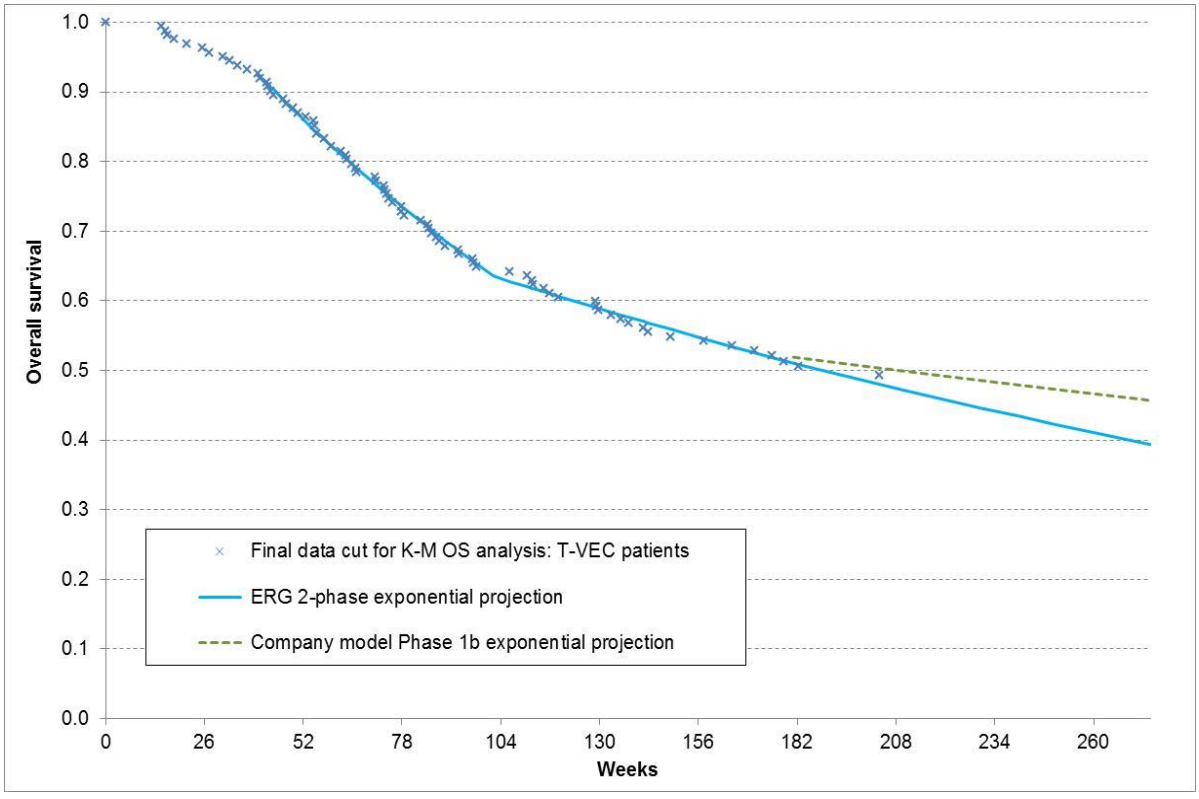


Figure 9 Comparison of company Phase 1b OS projection and ERG exploratory projection

5.7 Conclusions of the cost effectiveness section

In the absence of direct trial evidence for a clinically appropriate comparator, estimation of the relative cost effectiveness of T-VEC vs current clinical practice is rendered extremely difficult. The company's proposal for a constructed comparator, based on the pooling of data from two ipilimumab trials[19,22] adjusted for baseline characteristics and using a proportional hazard model derived from a patient population that is very different from *the T-VEC licensed population*, is considered by the ERG to be ill-conceived and unreliable as the basis for determining cost effectiveness. Moreover, due to the high degree of volatility exhibited in model-generated quantitative estimates of cost effectiveness when ERG amendments are implemented, the ERG does not consider that it is appropriate to present detailed alternative ICERs for this questionable comparison.

The ERG has also identified serious problems relating to the long-term projection of survival. These relate to the selective use of registry data and life table estimates. The company appeals to precedents from previous appraisals in melanoma to justify their approach to projecting survival. However, the ERG considers that the populations studied previously differ substantially from the target population proposed for T-VEC and from the population on which the Korn model[51] was based, so that the appeal to such precedents is not appropriate.

Had the OPTiM trial[4] included an alternative treatment arm involving a recognised alternative treatment (e.g. DTIC), then indirect evidence synthesis may have been appropriate. Unfortunately, it is not possible to determine whether GM-CSF constitutes an active or inactive comparator for T-VEC, so the data from the comparator arm of the OPTiM trial[4] can play no part in assessing the extent to which T-VEC benefits patients with non-visceral metastatic disease compared to current practice.

8 DISCUSSION

Evidence from the OPTiM trial

T-VEC *is licensed* for the treatment of patients with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, stage IIIC and stage IV M1a) with no bone, brain, lung or other visceral disease. In practice, the melanoma must also be injectable. Evidence for the efficacy of T-VEC treatment in this population has been obtained from a post-hoc analysis of data from patients with non-visceral metastatic disease who took part in the OPTiM trial[4].

The ERG considers that the efficacy results for the OPTiM trial[4] ITT population (a broader patient population that also includes patients with stage IV M1b and stage IV M1c disease), all of which favour T-VEC, may be subject to bias. This is because the trial lacked blinding, employed limited central assessment and the proportion of patients dropping out of the GM-CSF arm was higher than that associated with the T-VEC arm. All of these limitations also apply to the analyses carried out on data collected from the subgroup of patients with non-visceral metastatic melanoma, with the additional concern that these analyses were not pre-specified. The ERG notes that, for this non-visceral metastatic disease subgroup, the differences in treatment effect between the two trial arms, for all efficacy outcomes, were large. This suggests that, despite the identified limitations, for these patients, the conclusion that T-VEC is a more efficacious treatment option than GM-CSF may be credible. However, the ERG has concerns relating to the validity of this subgroup as it comprises both patients with stage III and stage IV disease. This is of concern as it is likely that the *differential survival trajectory* of patients differs by stage of disease which means this is not a relatively homogeneous patient group.

In summary, results from the OPTiM trial[4] show that T-VEC is clinically superior to GM-CSF. However, GM-CSF is not used in the NHS to treat patients with melanoma and, therefore, for the purposes of this STA, is not considered to be a relevant comparator

Applicability of the OPTiM trial results to clinical practice

The ERG considers that the characteristics of patients included in the OPTiM tria,[4] with non-visceral metastatic disease, are generally similar to the patient population likely to be considered for treatment with T-VEC in clinical practice in England. In this respect, the results from the OPTiM trial[4] are generalisable to patients seen in clinical practice in England.

Results from the OPTiM trial[4] show that, for patients treated with T-VEC, measures of ORR, DRR and TTF were better in the subgroup of patients with non-visceral metastatic disease than in the whole trial arm: 40.5% vs 26.4%, 25.2% vs 16.3% and 13.1 months vs 8.1

setting. In the FDA briefing document[37] it is suggested that the overall risk-benefit profile of T-VEC shows most benefit to patients receiving first-line treatment. Furthermore, within the draft SmPC,[36] there is a caution that the efficacy data supporting the use of T-VEC in second or later line treatment settings are limited.

The lack of confidence in the efficacy of T-VEC as a second (or later) line of treatment is largely due to the fact that, during the period when the OPTiM trial[4] was conducted, first-line treatment options for patients were different from those available to such patients today. This means that the patients in the OPTiM trial[4] who received T-VEC as a second- (or later) line of treatment will be different from the patients receiving T-VEC as a second- (or later) line of treatment in clinical practice today. In addition, it is reported in the draft EPAR[5] that there is a strong correlation between line of therapy and disease stage; line of therapy was not retained as an independent predictor for DR in a multivariate analysis considering disease stage.

Treatment with T-VEC can be continued even if there is some evidence of disease progression, with a minimum of 6 months of treatment being recommended. The EMA[5] raised concern that, for some patients, next-line treatment may commence later than if an alternative to T-VEC had been administered at the time of disease progression. The ERG considers that, because injectable melanoma entails lesions that can be clearly seen by the treating clinician, unnecessary treatment delays are unlikely since, if there is evidence of rapid progression, clinicians would not delay next-line treatment in clinical practice.

Company's cost effectiveness estimates

The ERG does not consider that the cost effectiveness results presented by the company are reliable. The reasons that support this conclusion relate primarily to the clinical evidence employed within the model and the methods used in the company model to project survival.

There are four main clinical issues that cast doubt on the reliability of the company's cost effectiveness results. The first issue is whether ipilimumab is the most appropriate comparator to include in the company's baseline cost effectiveness analysis. The second and third issues relate to factors that affect patients' *differential survival trajectory*, namely (a) that the subgroup of patients with injectable non-visceral metastatic disease includes both patients with stage III and those with stage IV disease, and (b) that this subgroup includes both patients receiving T-VEC as a first-line treatment and those receiving it as a later line of treatment. The fourth issue is that the relative clinical effectiveness of T-VEC compared with any treatment currently used in clinical practice is unknown.

Table 36 List of studies included in the evidence base for the modified Korn and two-step Korn models

Study	Treatments	Patient population
OPTiM trial[4]*	T-VEC GM-CSF	Previously treated and untreated patients with *stage IIIB* to stage IV M1c disease
MDX010-20[19]	Ipilimumab monotherapy ipilimumab in combination with gp100 gp100	Previously treated patients with stage III or stage IV disease
CA184-024[22]	Ipilimumab + DTIC DTIC monotherapy	Previously untreated with stage III or stage IV disease

Bristol-Myers Squibb=Bristol Myers Squibb; DTIC=dacarbazine; GM-CSF= granulocyte-macrophage colony-stimulating factor
*The company cites the primary reference for the OPTiM trial to be a 2014 conference abstract by Kaufman et al[48]
Source: CS, adapted from Table 4-22

11.2.1 The modified Korn model

The model originally reported by Korn[51] can be used to predict OS for melanoma patients using four prognostic characteristics; gender, ECOG PS, presence of visceral metastases, and presence of brain metastases. The coefficients for the effects of these variables on relative risk were obtained using prediction models based on individual patient data from 42 Phase II studies, in 2100 patients with metastatic melanoma, and are provided in Equation 1.

Equation 1)

$$\log(\widehat{HR}) = 0.248X_{Gender=Male} + 0.436X_{ECOG=1} + 0.948X_{ECOG\geq 2} \mp 0.421X_{Visceral=YES} + 0.304X_{Brain=YES}$$

The proportion of patients with each specified characteristic are inputted into the equation in order to give the log(HR) for each treatment group.

However, the company decided that a modified Korn model, which would take elevated LDH levels into consideration as a prognostic factor, was more appropriate to adjust the data as elevated LDH levels has been found to be an important independent prognostic factor in metastatic melanoma.[52] Bristol-Myers Squibb developed such a model in their recent submission to NICE for the use of ipilimumab in previously untreated metastatic malignant melanoma.[11] The modified Korn equation with the estimated coefficients is:

Equation 2)

$$\log(\widehat{HR}) = -0.154X_{Gender=Female} - 0.400X_{ECOG=0} - 0.285X_{Visceral=NO} - 0.306X_{Brain=NO} - 0.782X_{LDH=Normal}$$