STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Talimogene laherparepvec for treating metastatic melanoma [ID508]

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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

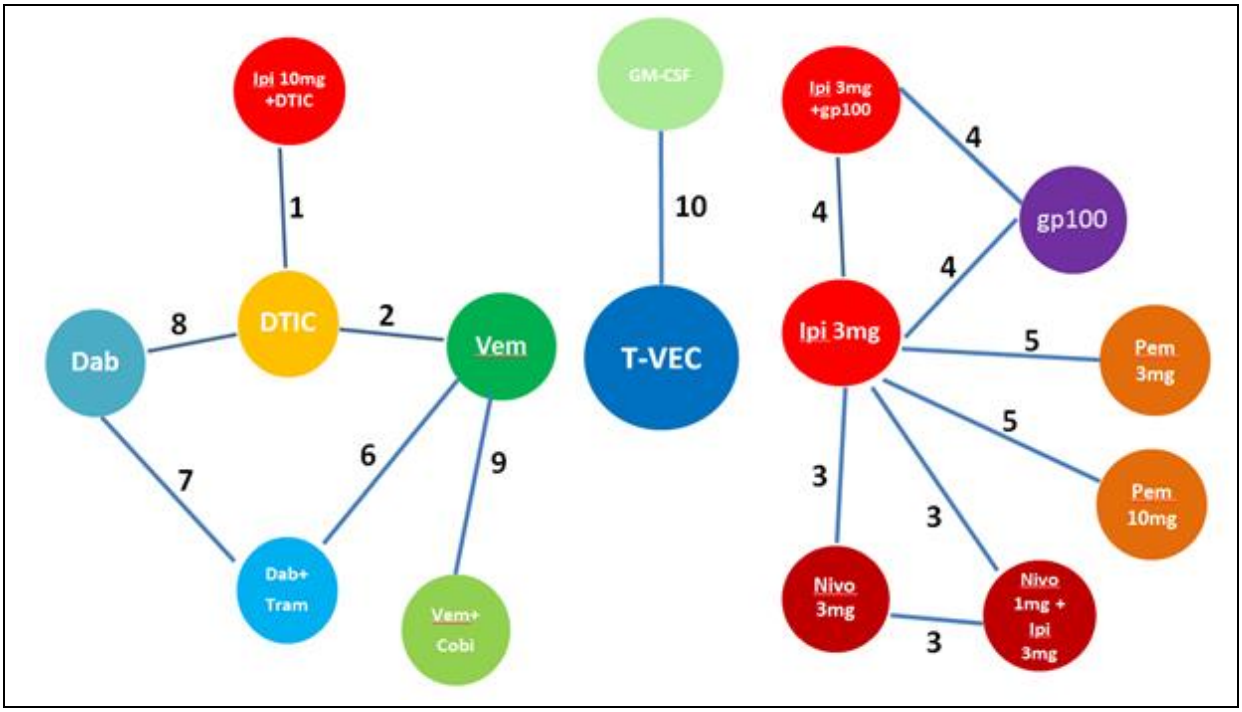


Figure 1 Network of evidence relevant to the decision problem
Note: Numbers correspond to # in Table 11 of this ERG report
Cobi=cobimetinib; dab=dabrafenib; DTIC=dacarbazine; GM-CSF=granulocyte macrophage colony-stimulating factor; gp100=glycoproteind100; nivo=nivolumab; ipi=ipilimumab; pem=pembrolizumab; 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:

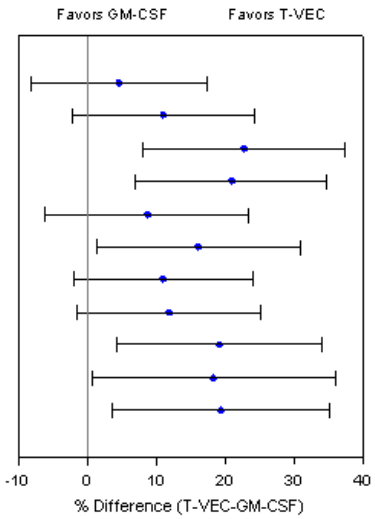
7. Overall quality of life [QoL]
8. Pain
9. Ability to work

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.

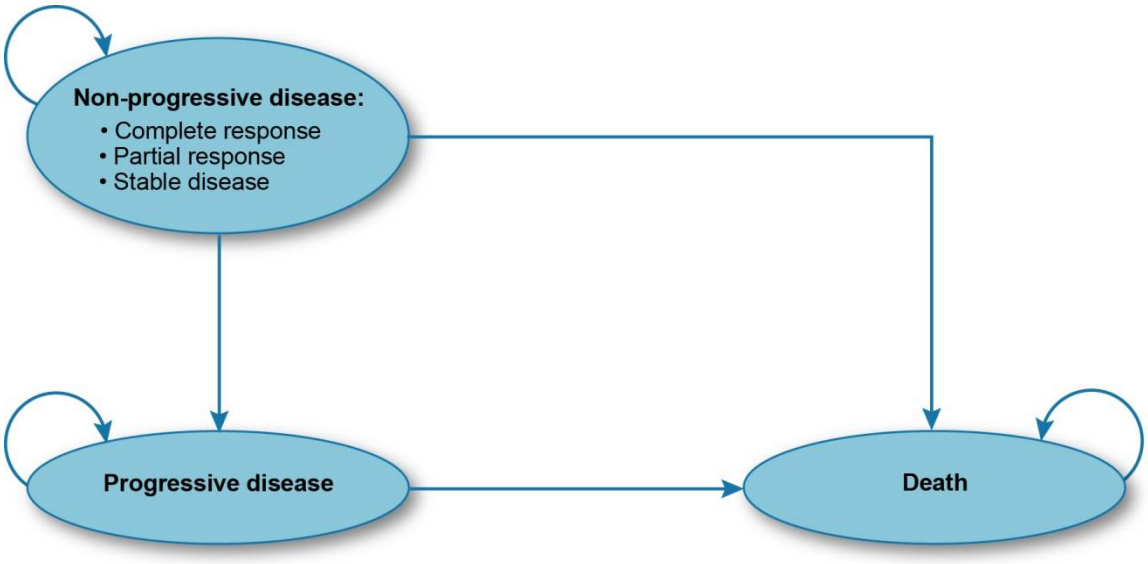


Figure 3 Schematic of company model

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%).

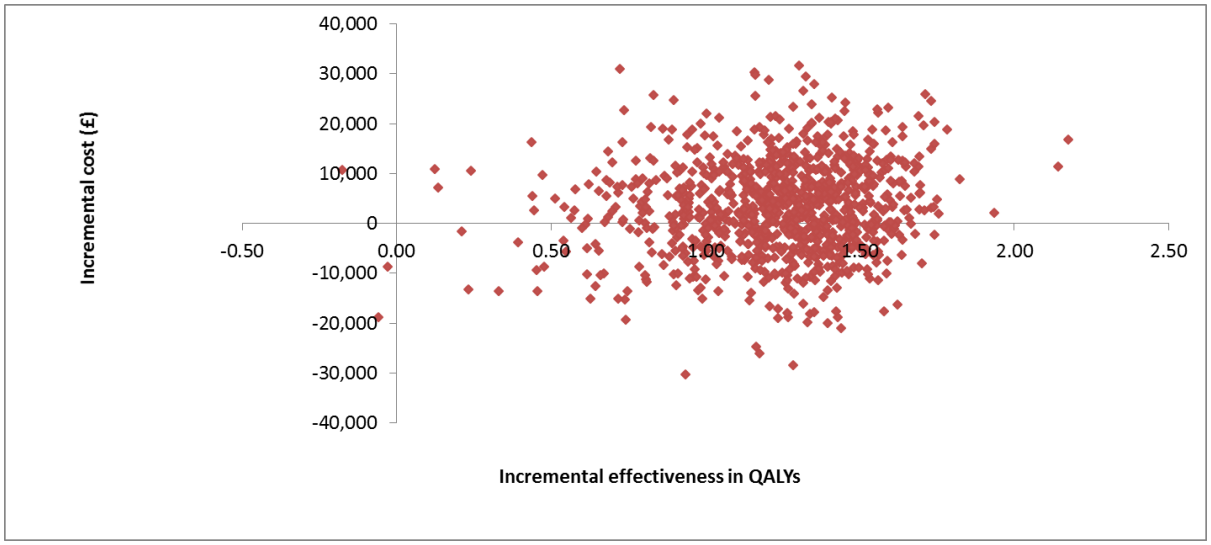


Figure 4 Cost effectiveness plane - modified Korn model
Source: Company model

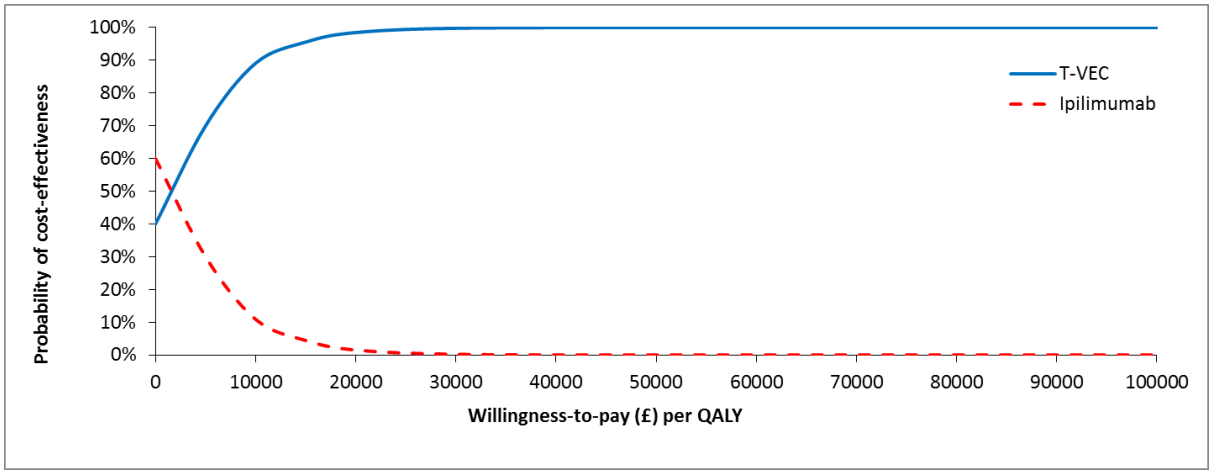


Figure 5 Cost effectiveness acceptability curve - modified Korn model (willingness-to-pay threshold £20,000)
Source: CS, Figure 5-42

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%).

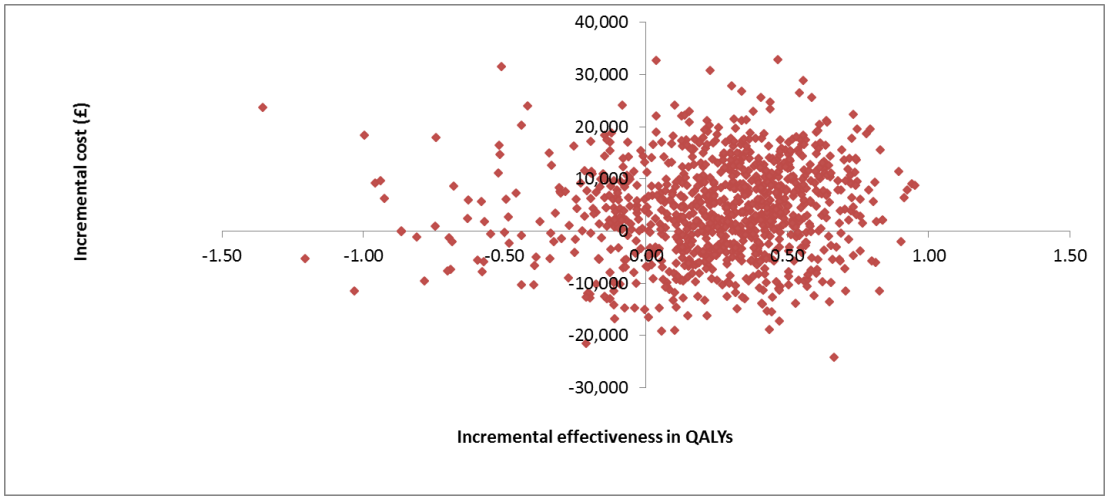


Figure 6 Cost effectiveness plane (two-step Korn model)
Source: Company model

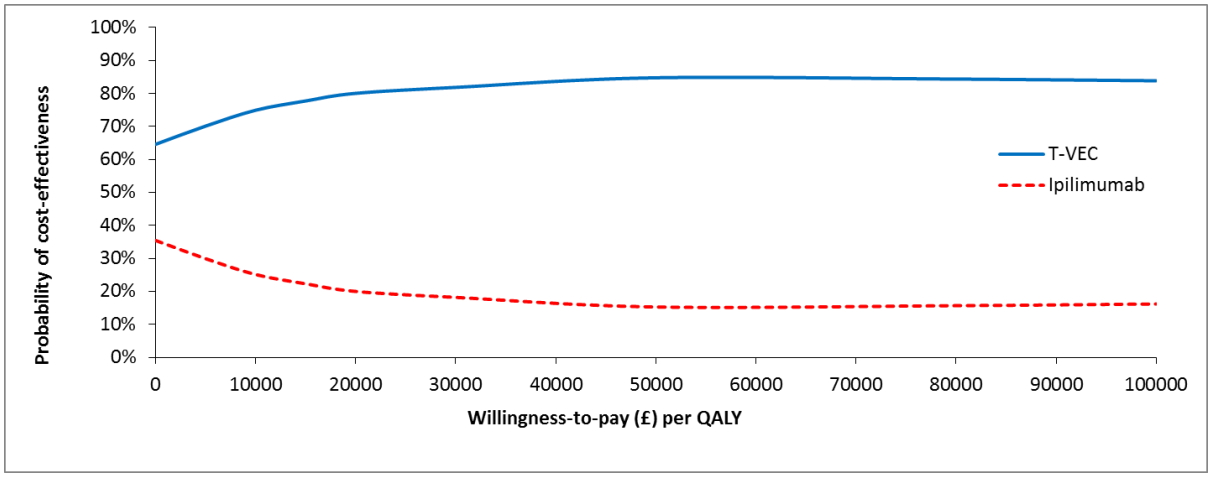


Figure 7 Cost effectiveness acceptability curve (two-step Korn model)

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.

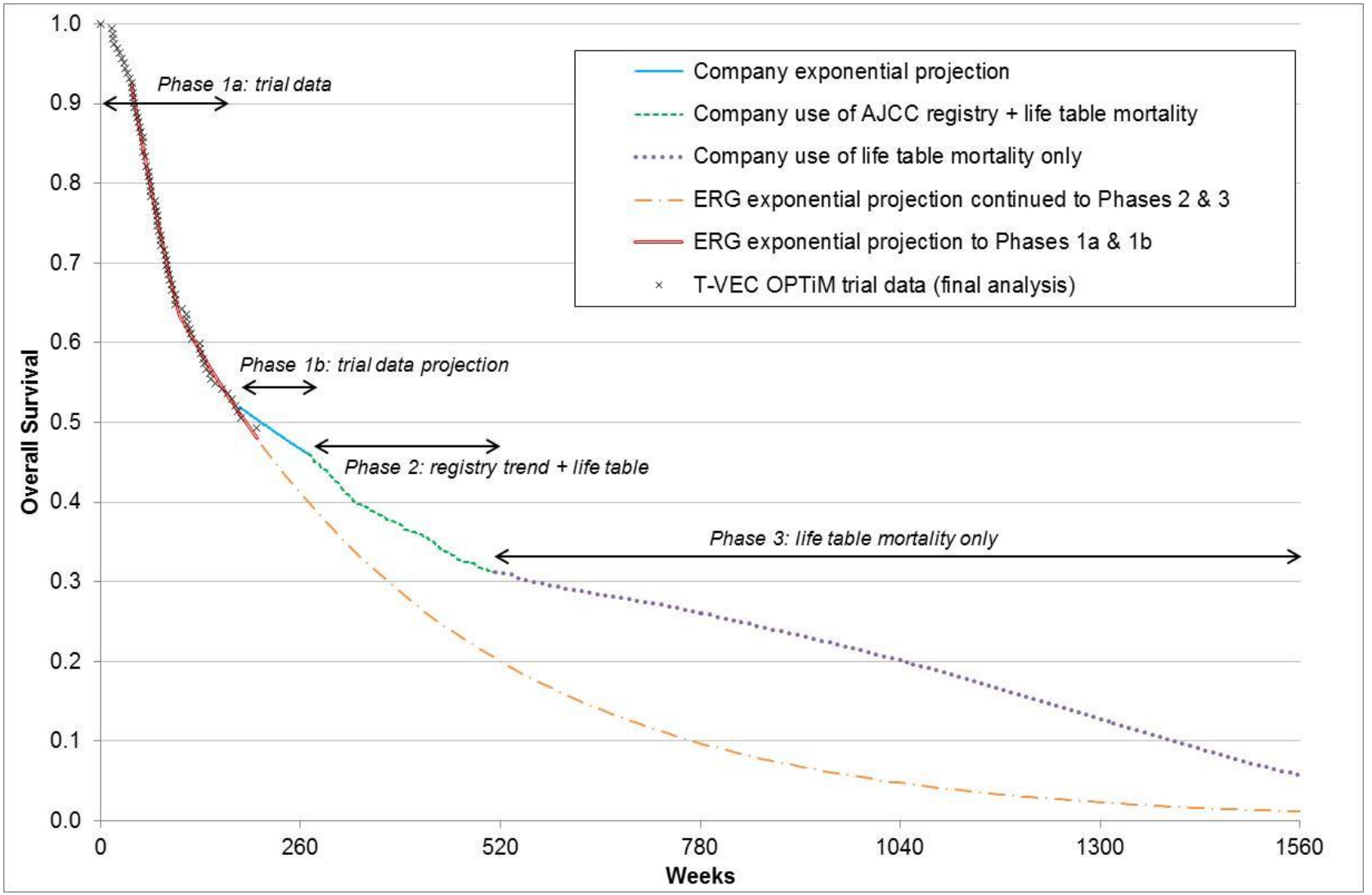


Figure 8 Company long-term T-VEC OS projection compared to ERG simple exponential alternative projection

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).

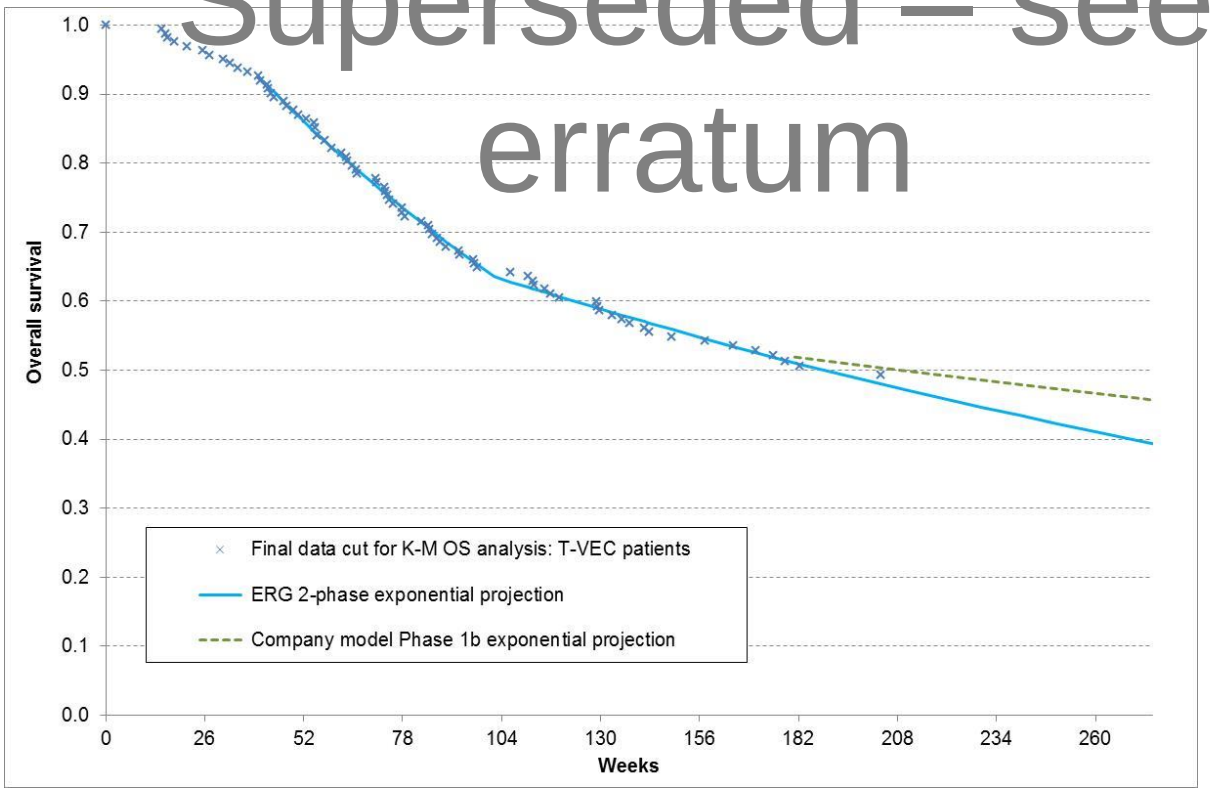


Figure 9 Comparison of company Phase 1b OS projection and ERG exploratory projection

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.

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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.

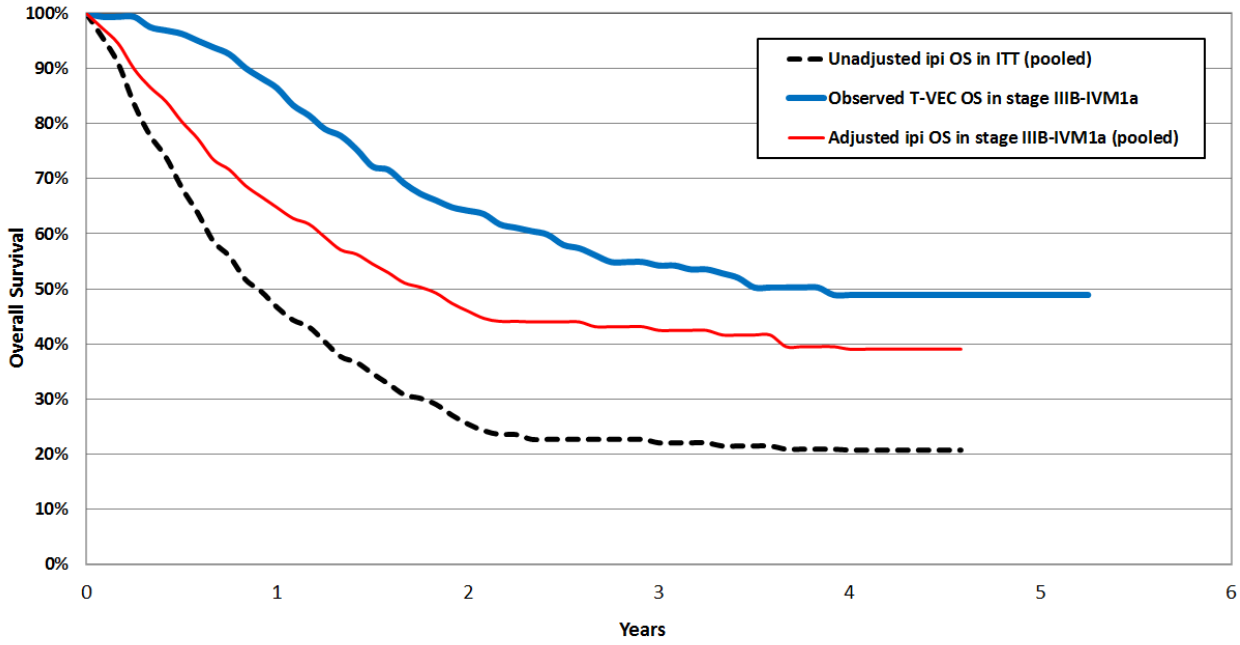

Figure 10 Modified Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

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.

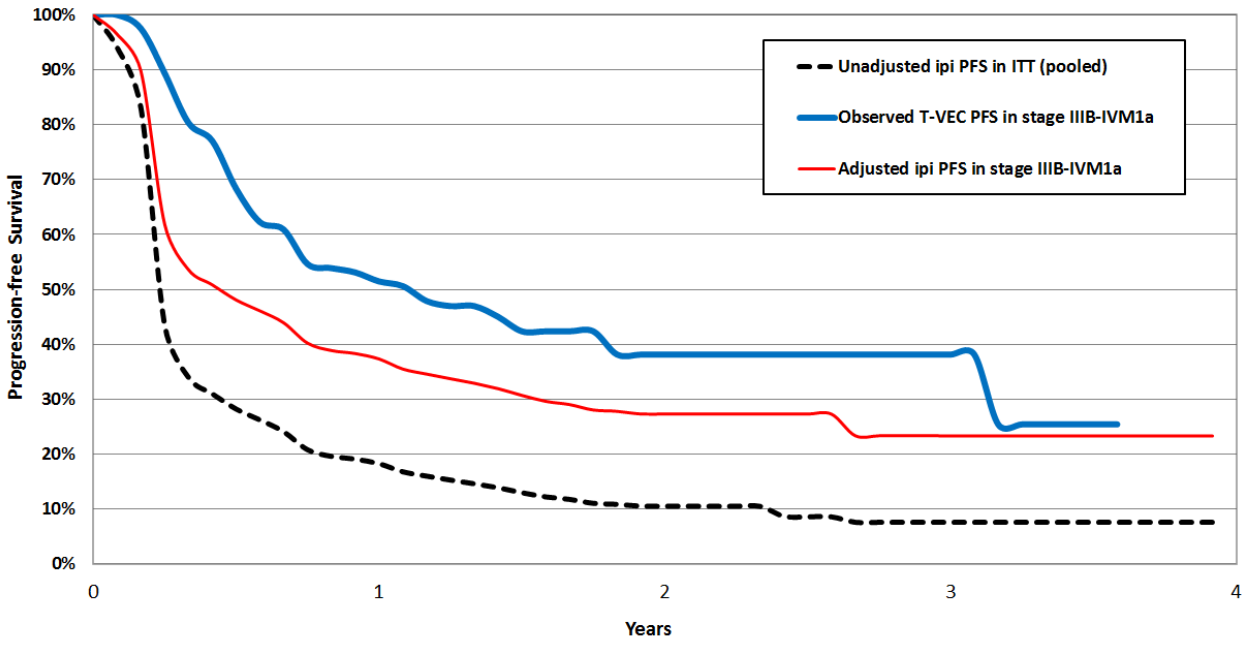

Figure 11 Modified Korn adjusted PFS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

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.

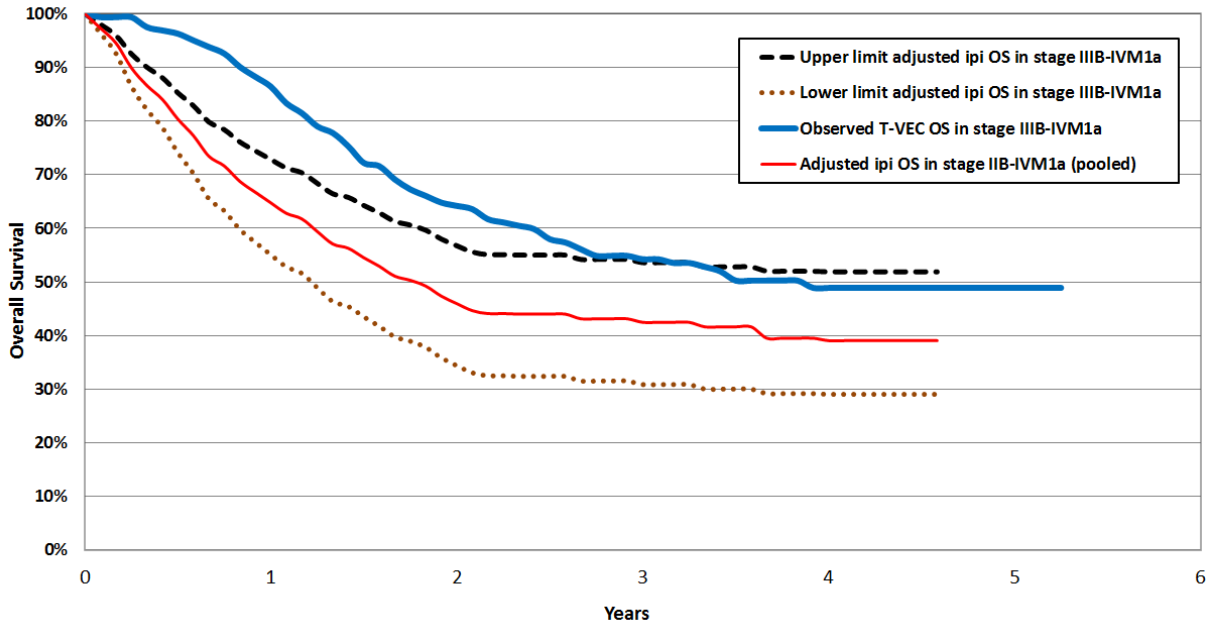

Figure 12 95% prediction interval around the modified Korn adjustment for ipilimumab OS

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.

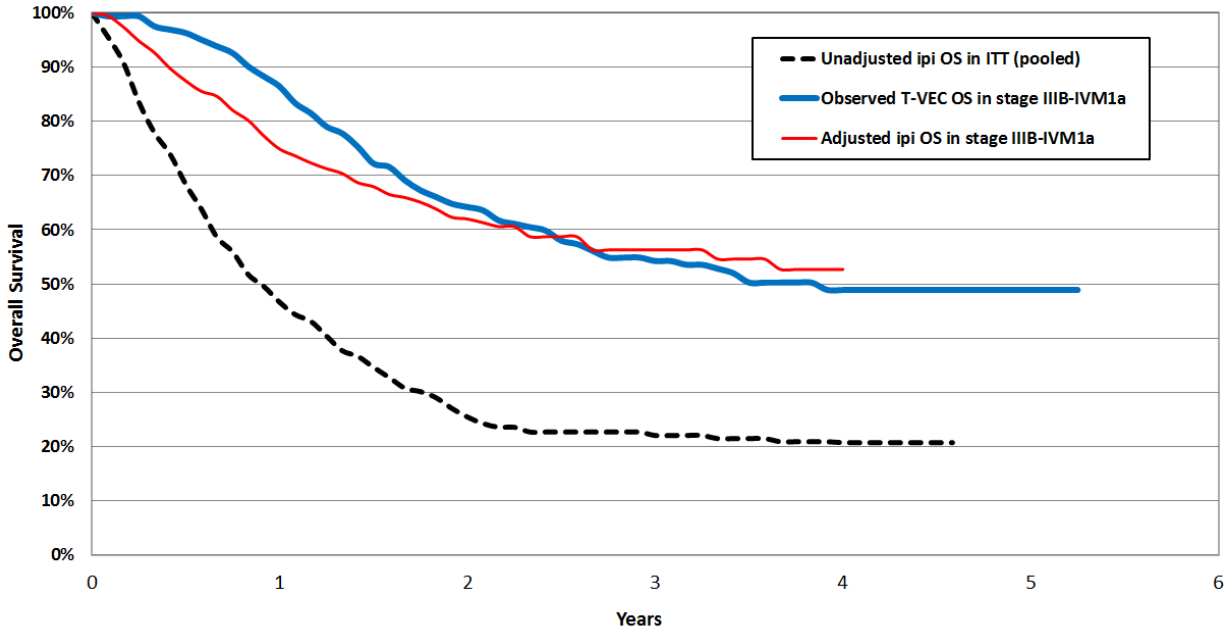

Figure 13 Two-step Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

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.

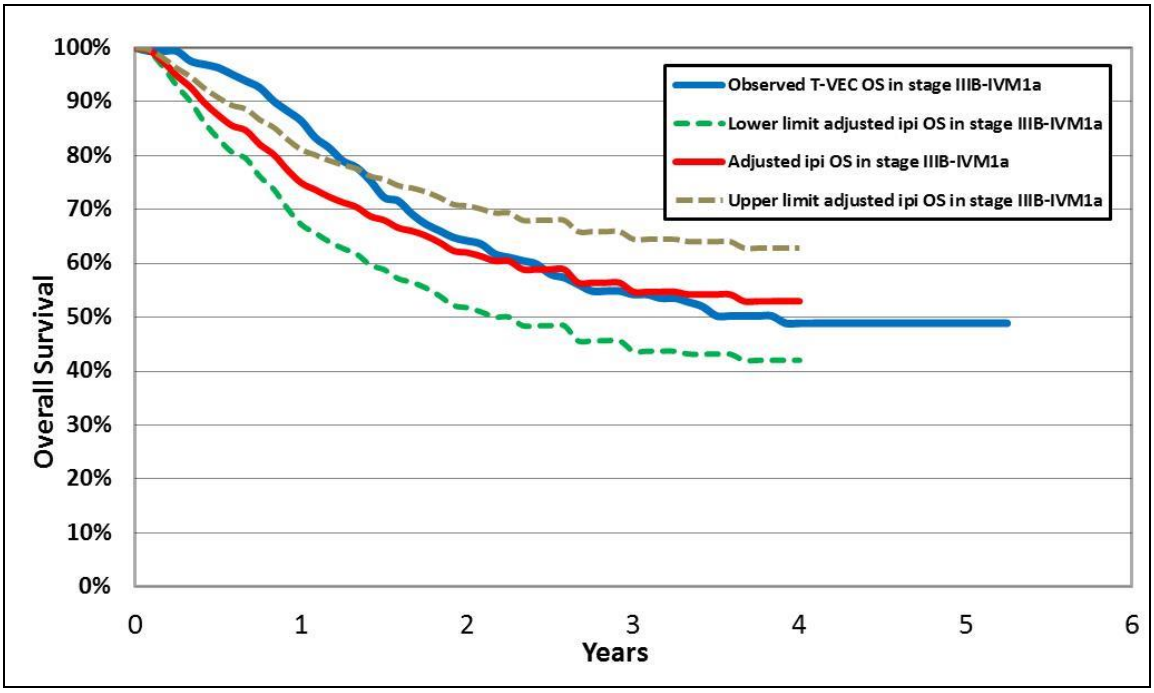

Figure 14 Two-step Korn model OS curve for ipilimumab in patients with stage IIIB to stage IV M1a disease

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.

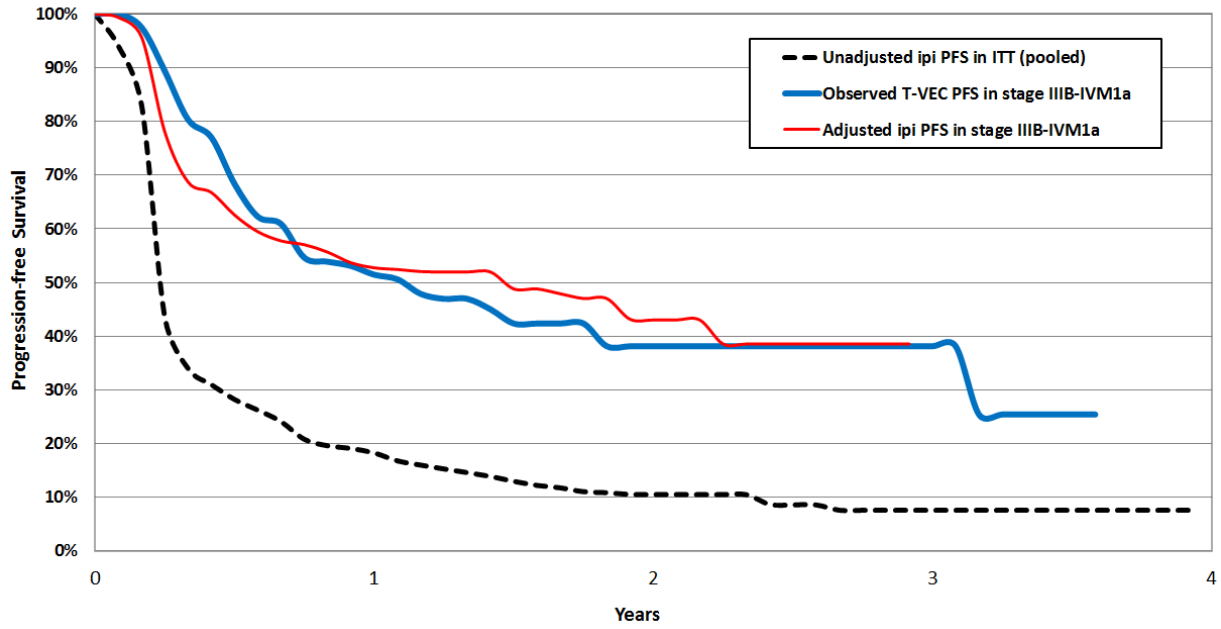

Figure 15 Two-step Korn model PFS curve for ipilimumab in patients with stage IIIB stage IV M1a disease

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.

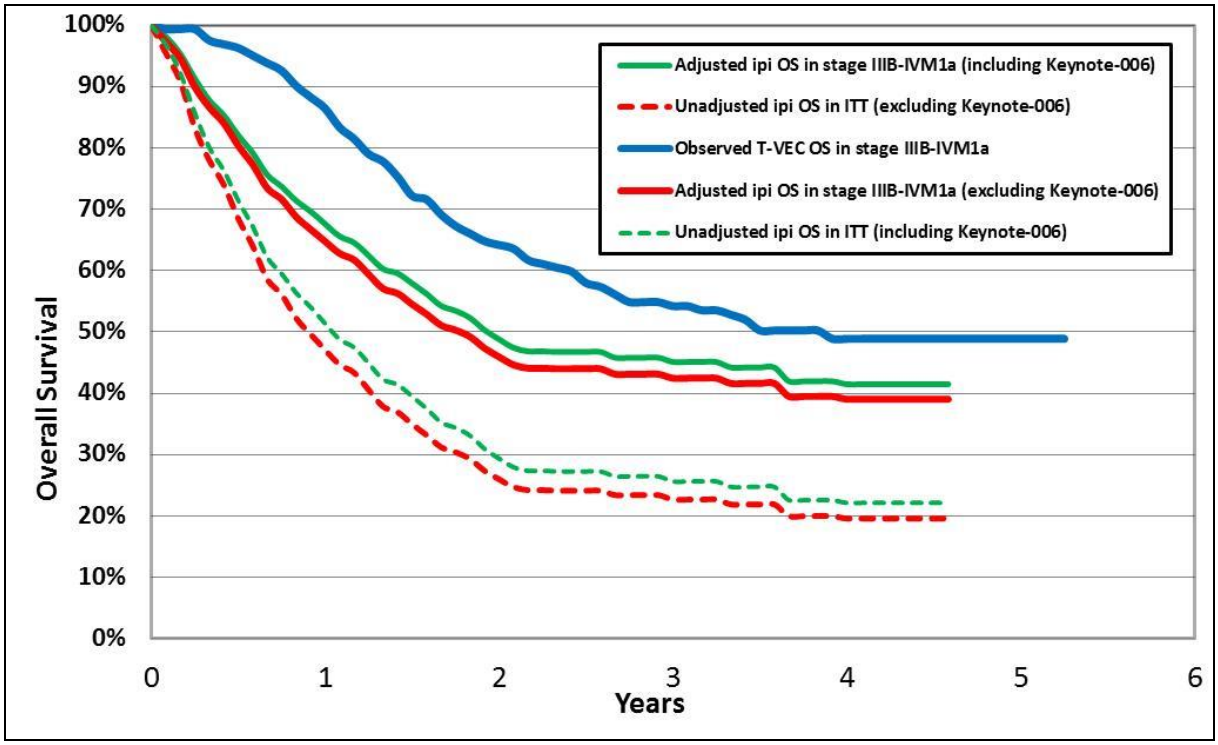

Figure 16 OS curves including KEYNOTE 006 trial using modified Korn model

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

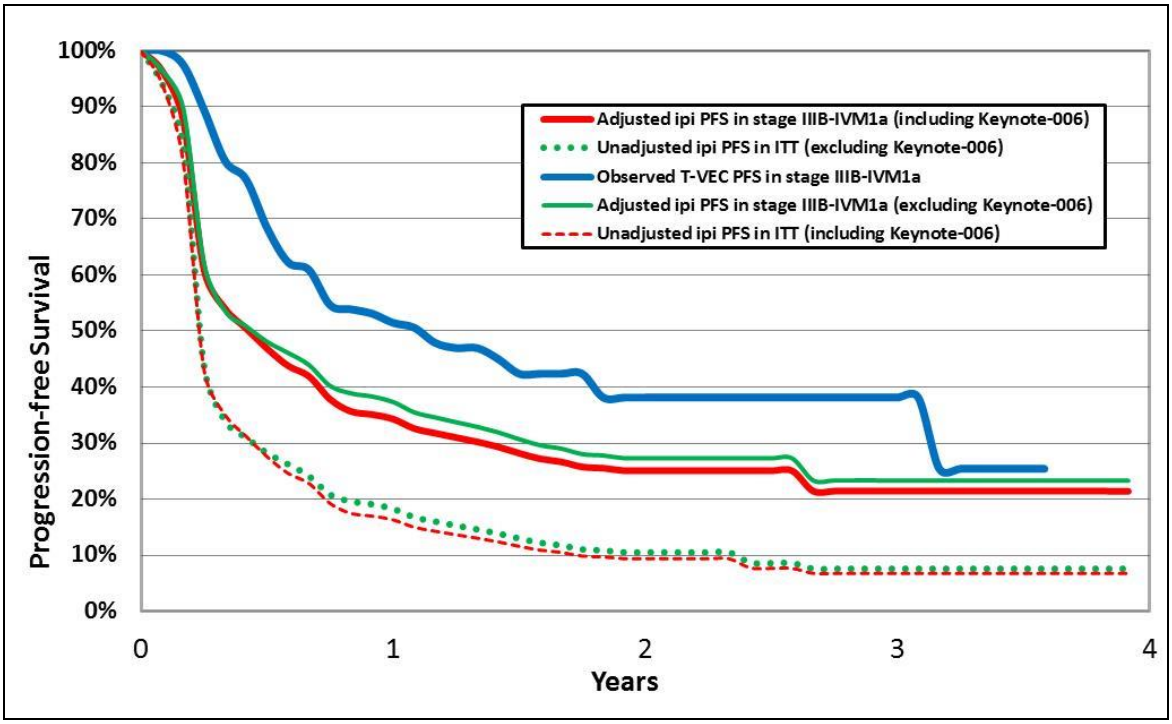

Figure 17 PFS curves including KEYNOTE 006 trial using modified Korn model

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.