NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma

Company evidence submission

Amgen Limited

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Abbreviations

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

1 Executive summary

Introduction

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

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

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

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

1.1 Statement of the decision problem

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

Table 1-1: The decision problem

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

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

1.2 Description of the technology being appraised

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

Table 1-2: Description of technology being appraised

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

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

1.3 Summary of the clinical effectiveness and safety/tolerability analysis

Summary of evidence and methods

T-VEC RCT and non-RCT evidence

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

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

Evidence and methods for indirect comparisons

Network meta-analysis Feasibility Assessment

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

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

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

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

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

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

Efficacy

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

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

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

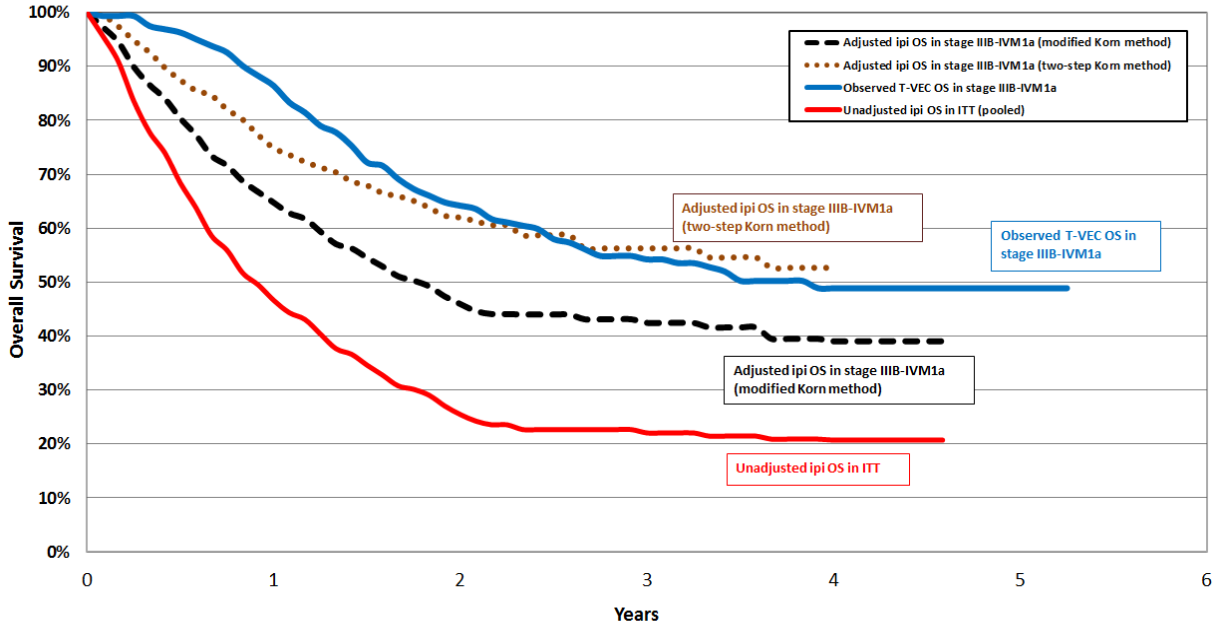
Safety

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

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

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

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



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

Strengths and limitations of the evidence base

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

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

Summary of clinical evidence

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

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

1.4 Summary of the cost-effectiveness analysis

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

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

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

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

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

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

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

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

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

Conclusion

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

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

2 The technology

2.1 Description of the technology

Brand name

Imlygic®

Approved name

Talimogene laherparepvec (T-VEC)

Therapeutic class

Oncolytic immunotherapy

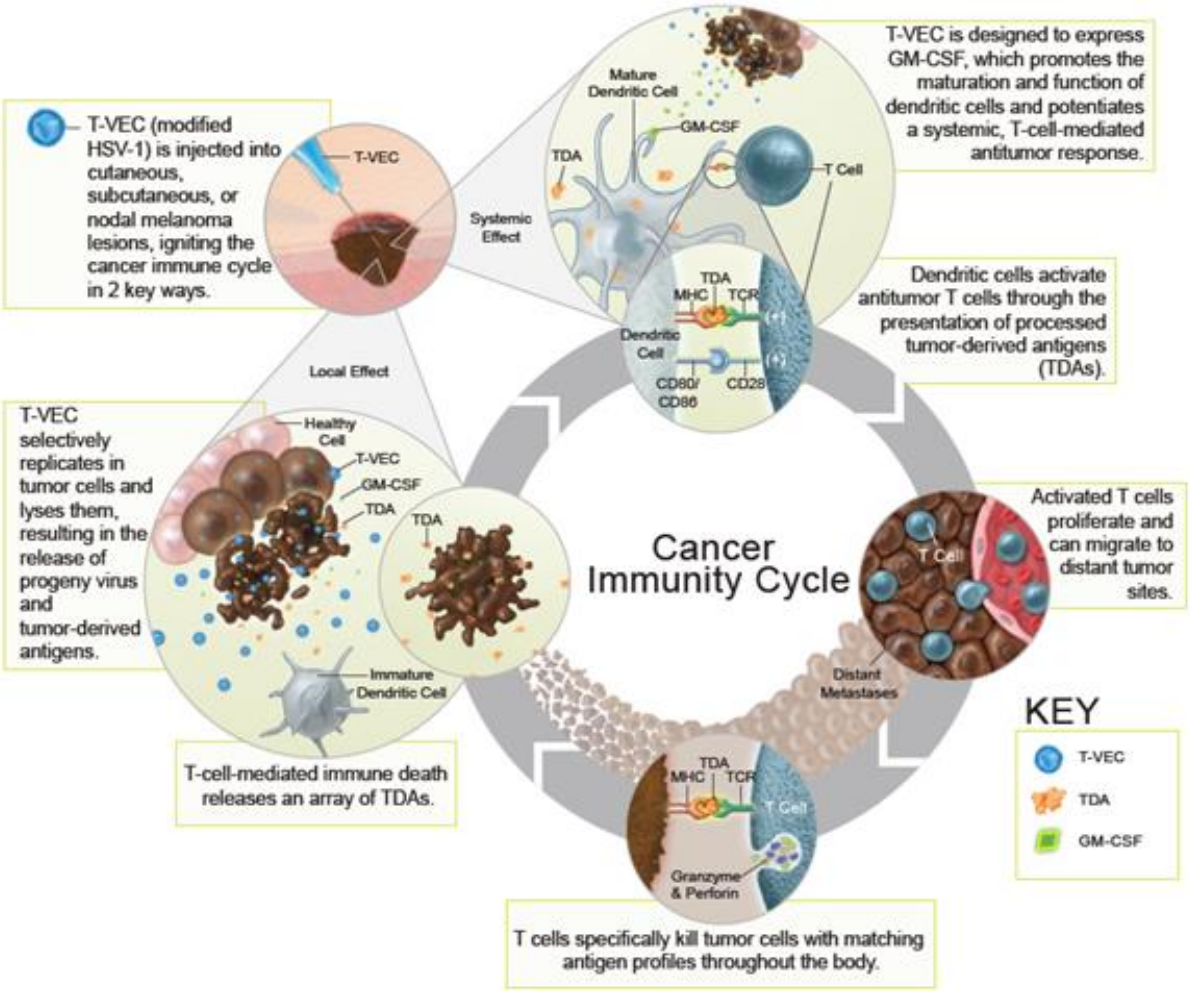
Mechanism of action

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

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

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

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

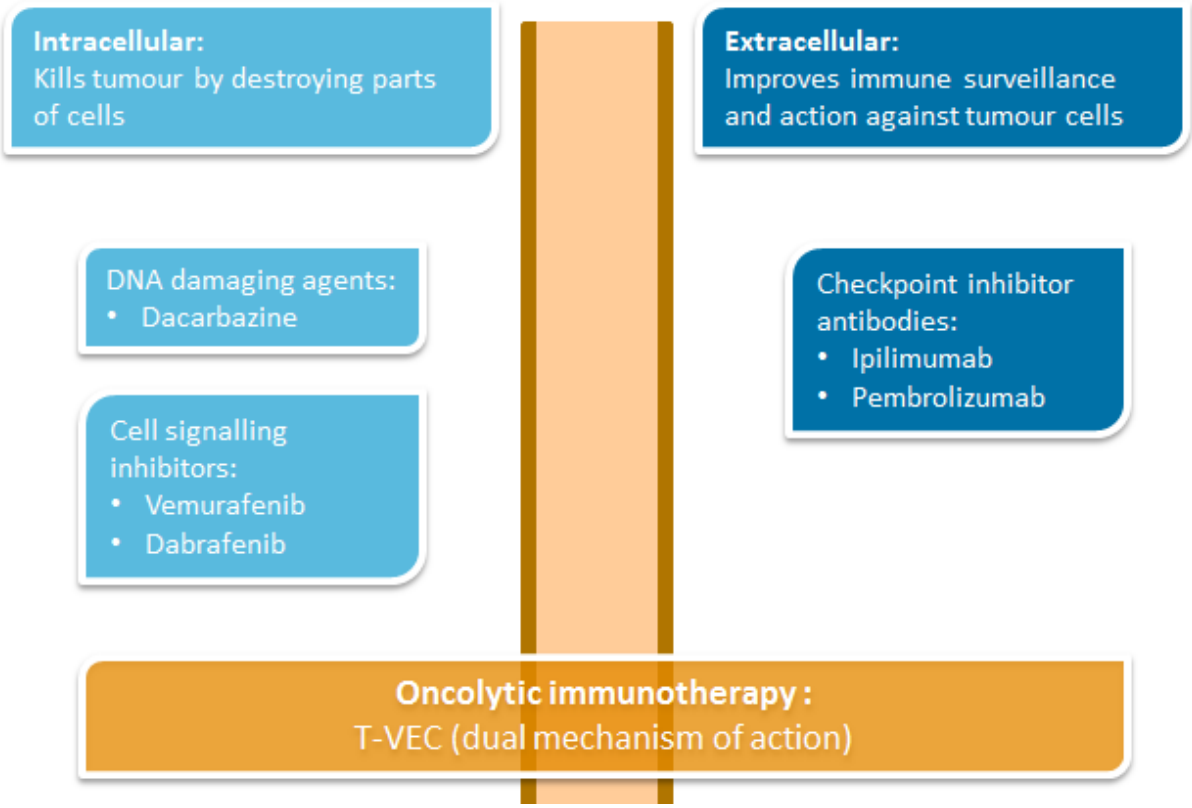


GM-CSF, granulocyte-macrophage colony stimulating factor; HSV-1, herpes simplex virus type-1; MHC, major histocompatibility complex; TCR, toll-cell receptor; TDA, tumour-derived antigens; T-VEC, talimogene laherparepvec

Source: Andtbacka et al 2014[5]

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

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



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

T-VEC, talimogene laherparepvec

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation

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

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

Main issues discussed by the regulatory organisation

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

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

Regulatory approval outside the UK

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

Other health technology assessments (HTAs) in the UK

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

2.3 Administration and costs of the technology

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

Table 2-1: Costs of the technology being appraised

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

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

2.4 Changes in service provision and management

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

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

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

2.5 Innovation

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

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

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

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

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

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

3.1 Overview of malignant melanoma

Pathophysiology

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

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

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

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

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

Disease staging

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

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

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

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

Incidence and survival

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

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

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

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

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

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

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

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

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

3.3 Description of clinical pathway of care

Aims of therapies

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

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

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

Description of current treatment options

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

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

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

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

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

Summary of NICE clinical guidelines, guidance and local guidelines

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

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

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

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

NICE TAs in development for metastatic melanoma

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

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

Other clinical treatment guidelines

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

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

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

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

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

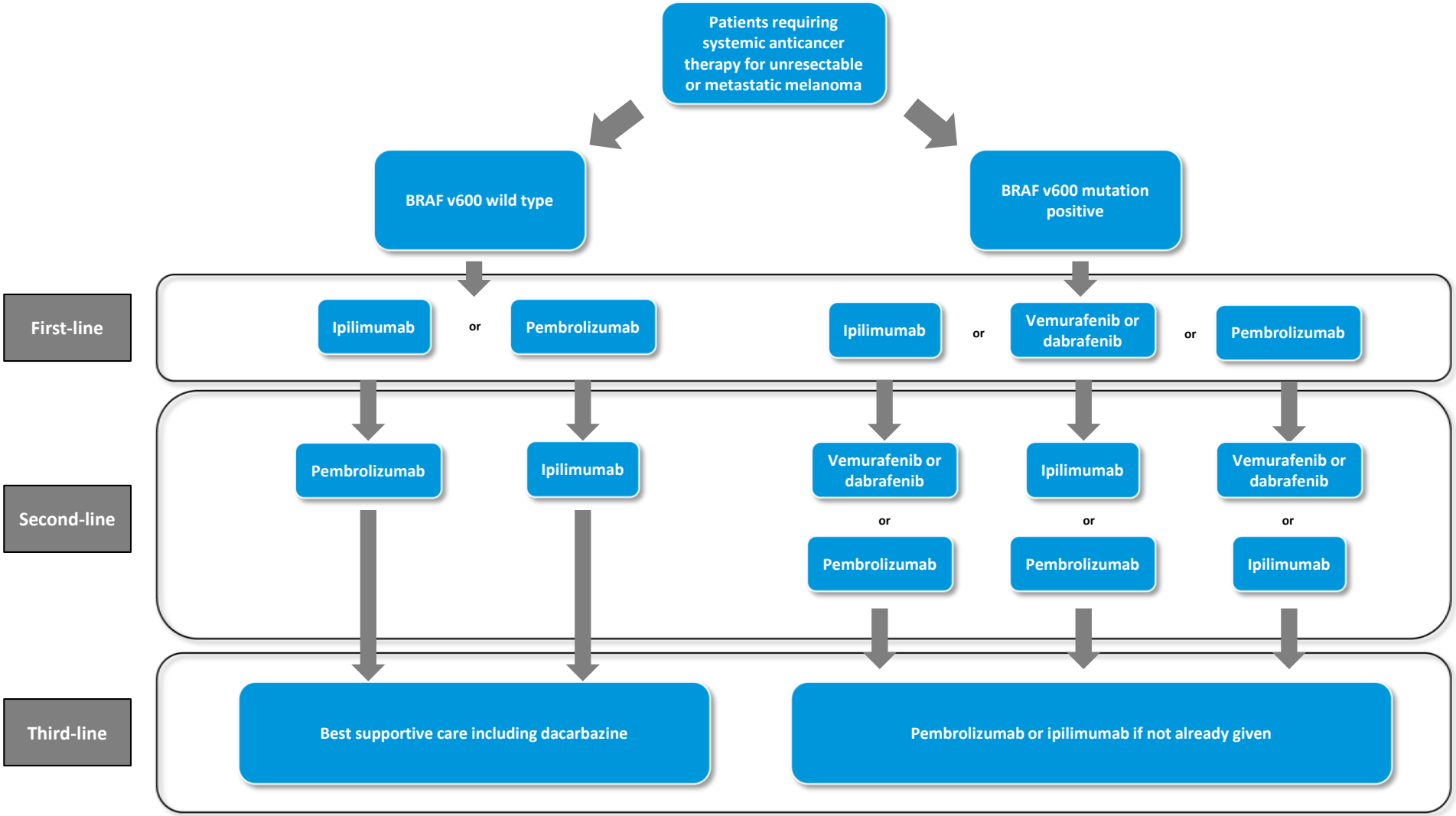
Clinical pathway of care showing the context of the proposed use of the technology

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

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

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

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



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

Limitations of current clinical treatment pathway

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

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

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

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

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

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

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

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

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

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

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

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

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

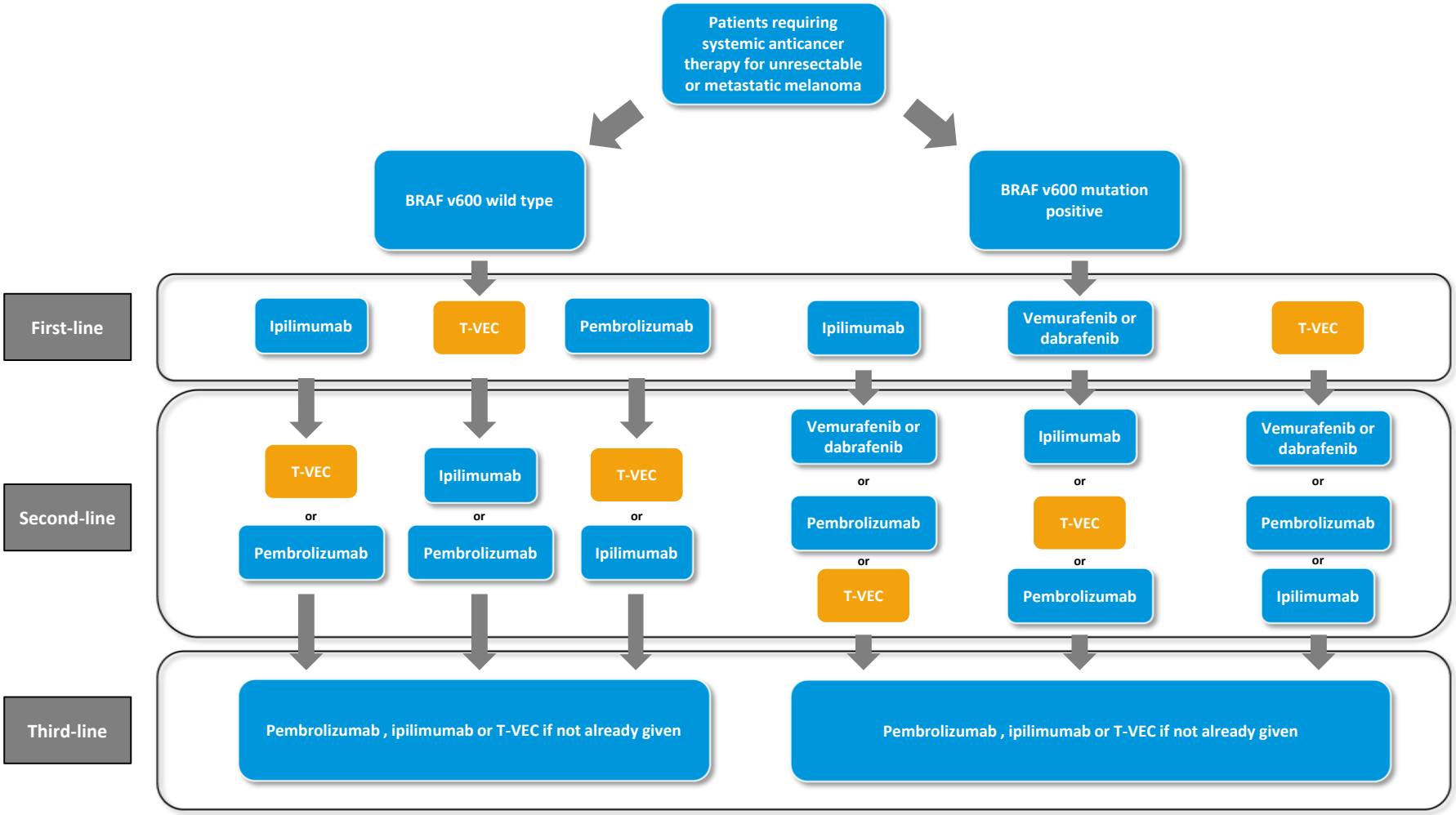
Proposed positioning within the treatment pathway and patient populations

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

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

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

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



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

Selection of Comparators

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

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

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

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

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

3.4 Life expectancy of patients with the disease

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

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

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

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

3.5 Equality Issues

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

4 Clinical effectiveness

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

4.1 Identification and selection of relevant studies

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

Search strategy

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

The following databases were searched for relevant studies:

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

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

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

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

American Society of Clinical Oncology (ASCO)

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

European Society for Medical Oncology (ESMO)

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

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

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

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

European Association of Dermato Oncology (EADO)

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

European Cancer Congress (ECC)

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

All search strategies are provided in Appendix 1.2.

Study selection

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

Table 4-1: Study inclusion and exclusion criteria

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

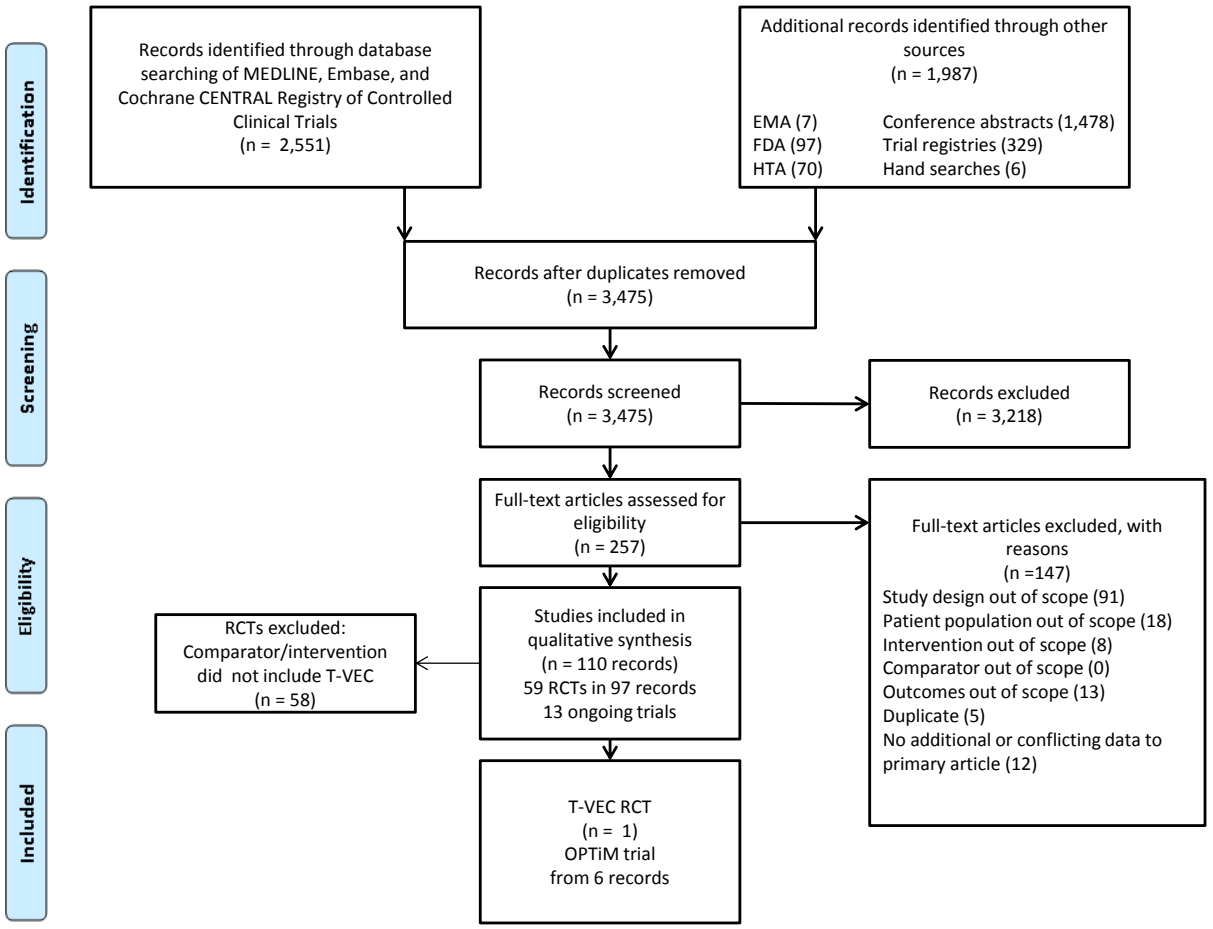
Abbreviations: HRQoL, health-related quality of life; RCT, randomised controlled trial; T-VEC, talimogene laherparepvec

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

Study selection results for RCT evidence

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

Figure 4-1: PRISMA flow diagram for RCT evidence

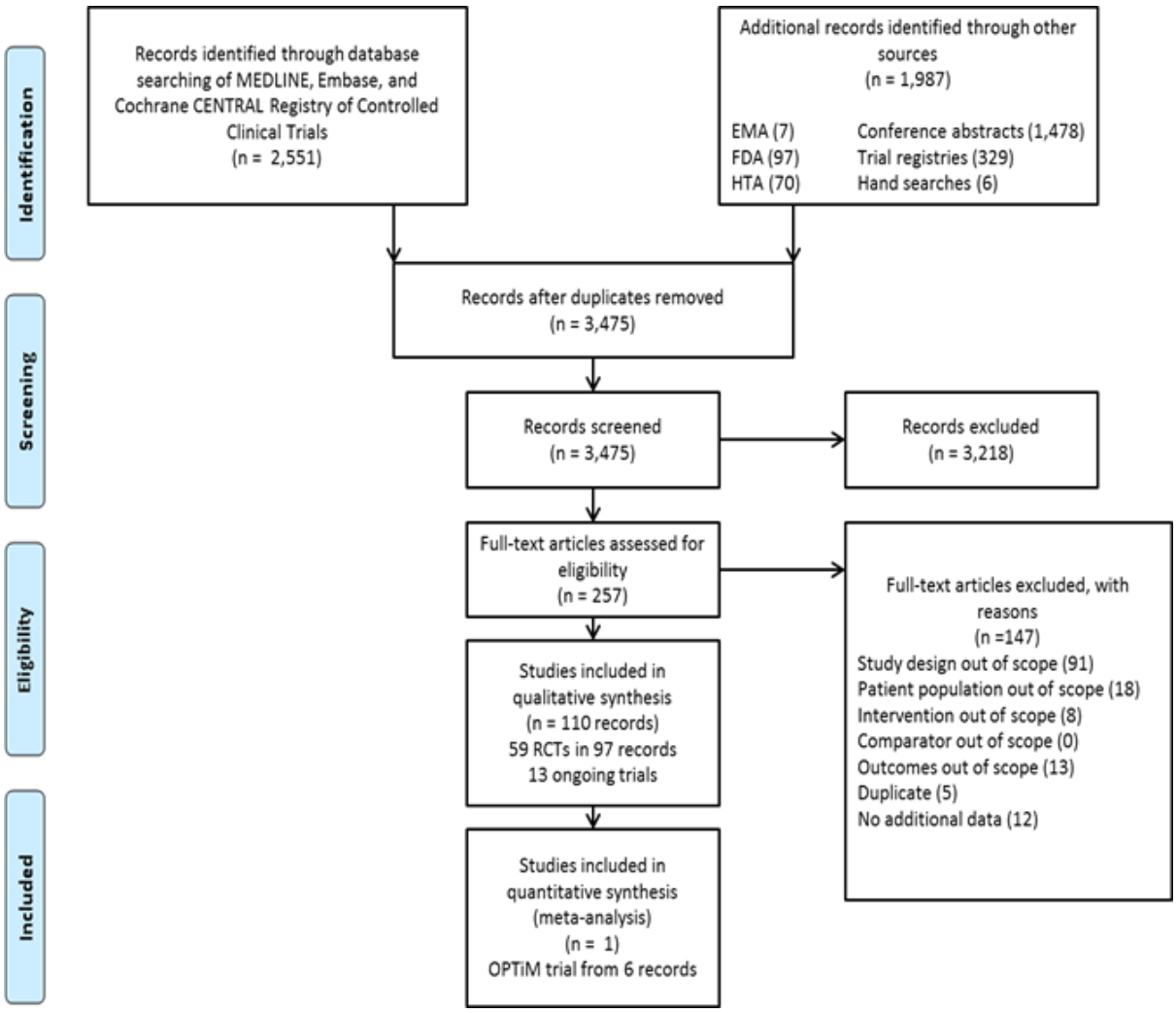


EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; RCT, randomised clinical trial

Study selection results for non-RCT evidence

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

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



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

4.2 List of relevant randomised controlled trials

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

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

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

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

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

4.3 Summary of methodology of the relevant OPTiM RCT

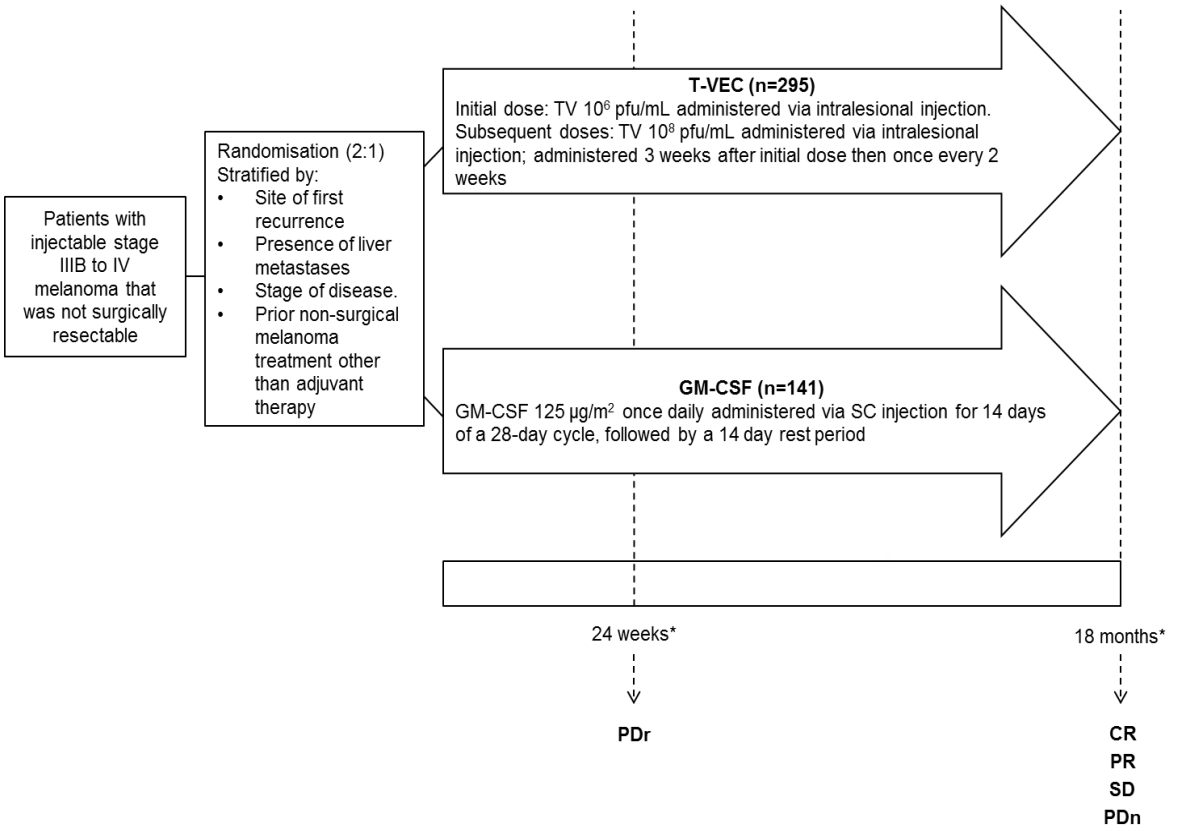
For the relevant RCT, OPTiM, a summary of trial design and methodology is presented in Table 4-3 and Figure 4-3, respectively.

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

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

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

Figure 4-3: OPTiM study design



Reference: OPTiM CSR[80]

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

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

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

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

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

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

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

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

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

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

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

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

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

References: Andtbacka et al[79]; OPTiM[80]
* Prolongation in INR, PT, and PTT when the result is from therapeutic anticoagulation treatment are permitted for patients whose injectable lesions are cutaneous and/or subcutaneous such that direct pressure could be applied in the event of excessive bleeding.
ALT, alanine amino transferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating factor; HIV, human immunodeficiency virus; INR, international normalised ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; T-VEC, talimogene laherparepvec; ULN, upper limit of normal

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

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

Endpoint	Definition	Assessed by
Response interval	Defined as the time from the date of randomisation to the date of the last documented evidence of response prior to any new anti-cancer therapy which may be given. Response interval will be zero if no response was ever achieved. This allows all randomised patients to be included in the analysis but post onset of response will be censored if the patient is still in response at the last observation, which may extend beyond the planned study duration for however long the patient is followed	Investigator
Safety endpoints		
Safety	Assessments for safety included all randomised and treated patients. Patients who were randomised but withdrew from the trial before receiving any study treatment were excluded from the safety assessment, but were still followed for response and survival. Safety assessments were based on AEs, laboratory data, concomitant medications, the results of physical examinations and vital signs. Safety was evaluated using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0, based on recorded AEs, physical examinations, and clinical laboratory assessments. All AEs were coded according to Medical Dictionary for Regulatory Activities version 10.1 or later. If a patient experienced multiple events that map to a single AE, the greatest severity and strongest Investigator assessment of relation to study drug was assigned to the AE in order to summarise the findings for the purpose of comparing T-VEC and GM-CSF	Investigator
Exploratory endpoints		
Quality of life	To assess patient reported quality of life in patients treated with T-VEC and GM-CSF with a standardised instrument, the Functional Assessment of Cancer Therapy-biological response modifier (FACT-BRM) was used	Investigator
Impact of response and durable response on survival	The relationship between achieving a response and a durable response and subsequent survival prolongation was explored	Investigator
Influence of BRAF mutation status	Where information is available, exploratory analysis of treatment effects based on BRAF mutation status may be conducted	Investigator
Reference: OPTiM[80] AE, adverse event; CR, complete response; DRR, durable response rate; GM-CSF, granulocyte macrophage colony-stimulating factor; OS, overall survival; PDr, clinically relevant disease progression; PFS, progression-free survival; PR, partial response; TTF, time to treatment failure; T-VEC, talimogene laherparepvec		

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

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

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

Planned interim analyses included:

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

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

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

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

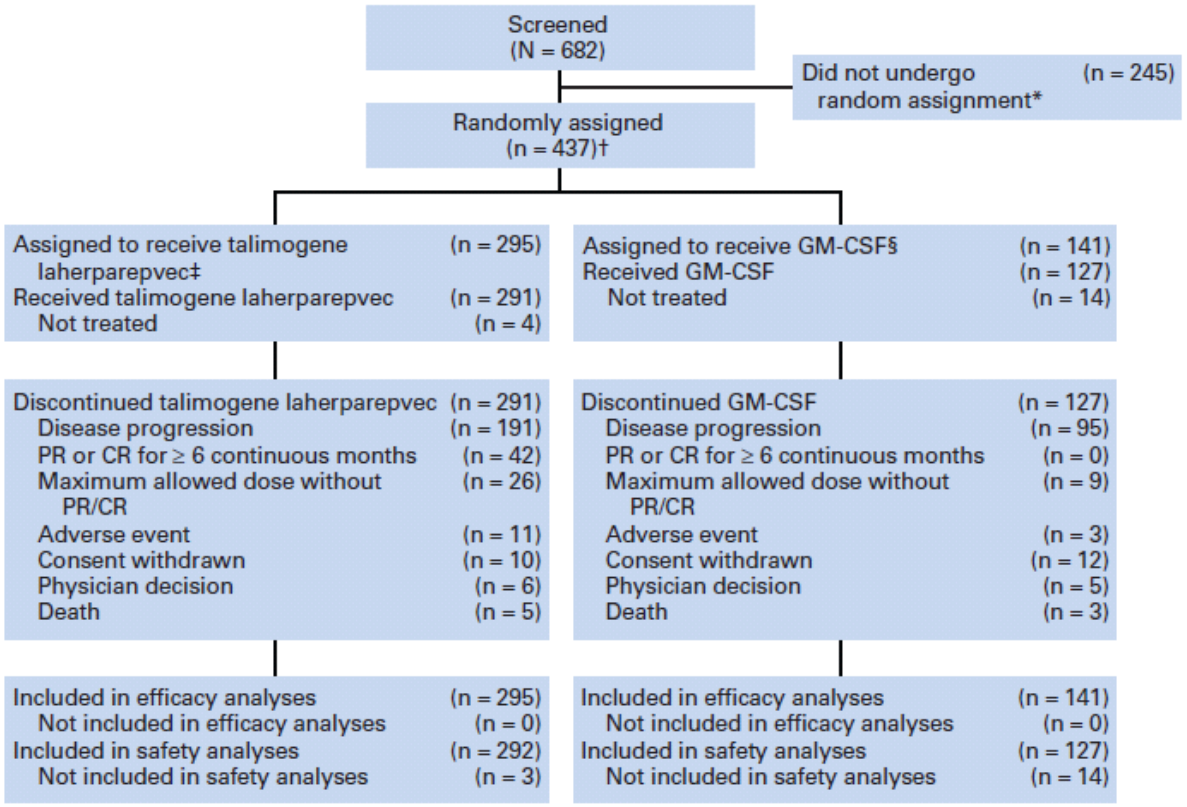
References: Andtbacka et al[79]; OPTiM[80]

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

4.5 Participant flow in the relevant OPTiM RCT

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

Figure 4-4: Patient disposition during the OPTiM study



Reference: Andtbacka et al 2015[79]

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

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

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

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

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

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

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

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

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

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

Reference: Amgen 2015 data on file[80] _ENREF_83

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

Baseline Patient Characteristics

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

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

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

Reference: Amgen data on file[80]

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

Treatment exposure

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

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

	Patients with stage IIIB-IVM1a disease	
	T-VEC (N=163)	**GM-CSF (N=76)**
Treatment duration (weeks)		
Mean	30	15
Median	26	10
Min-Max	4-79	1-58
Dose at cycle one, day one (mL)		
Mean	2.69	-
Median	3.00	-
Min-Max	0.5-4.0	-
Average dose volume post cycle one, day one (mL)		
Mean	2.60	-
Median	2.79	-
Min-Max	0.3-4.4	-
Cumulative volume (mL)		
Mean	37.04	-
Median	27.20	-
Min-Max	2.5-135.0	-
Number of injections		
Mean	15.4	-
Median	14.0	-
Min-Max	2-38	-
Reference: Amgen data on file[80] GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec		

Subsequent treatment in patients with stage IIIB-IVM1a disease

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

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

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

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

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

4.6 Quality assessment of the relevant OPTiM RCT

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

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

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

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

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

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

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

4.7 Efficacy results of the relevant OPTiM RCT

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

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

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

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

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

Primary endpoint

Durable Response Rate (per EAC assessment)

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

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

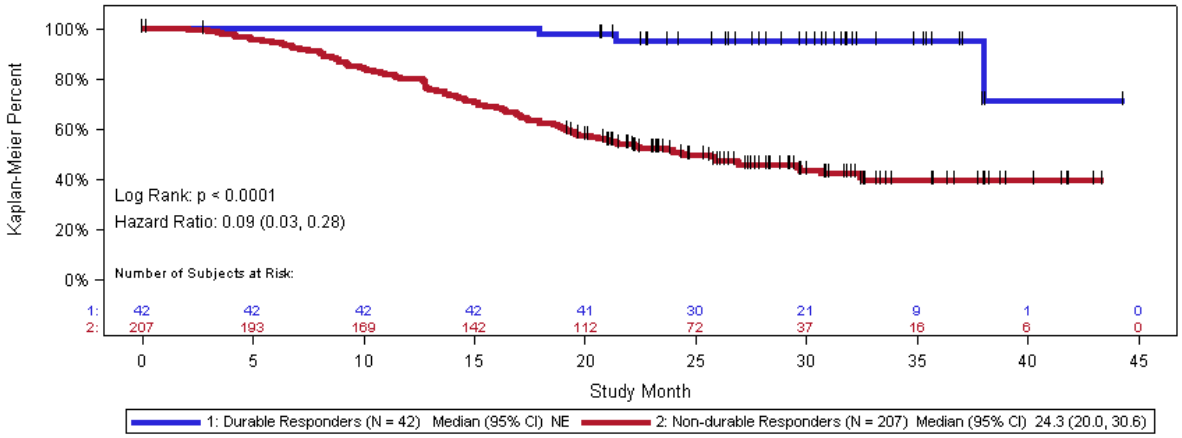
0.17-0.65), P=0.0007 and patients with a DR had a higher quality of life improvement rates versus patients with no DR: odds ratio (DR vs no DR) = 2.8 (95% CI: 1.1-7.0), P=0.0247.

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

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

References: Harrington 2015[82]; Amgen data on file[80]
[a] The Clopper-Pearson method was used to calculate exact CIs for binary endpoints. Wilson's score method with continuity correction was used to calculate an approximate CI for between-group differences in binary rates
[b] Using Fisher's Exact Test
[c] Obtained from a logistic regression model with logit link. An odds ratio >1.0 indicates a higher DRR for T-VEC relative to GM-CSF
CI, confidence interval; DRR, durable response rate; EAC, Endpoint Assessment Committee; GM-CSF, granulocyte macrophage colony-stimulating factor T-VEC, talimogene laherparepvec

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



Subjects that have not been recorded as dead are included as censored
ITT population includes ass subjects who have been randomised to receive study treatment. OS is calculated as the number of months from randomisation date to death date or last known to be alive date
CI, confidence interval; NE, non-estimable; OS, overall survival

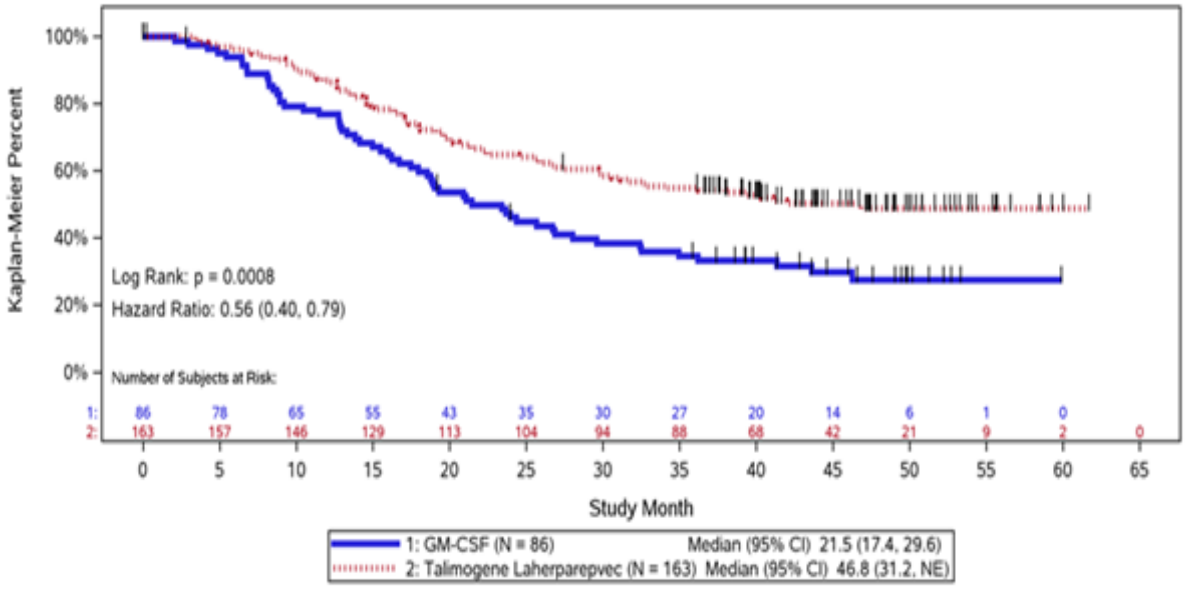
Secondary endpoints

Overall survival (OS)

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

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

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



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

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

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

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

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

References: OPTiM[80]; Kaufman et al 2014[84]; Harrington et al 2015[82]
[a] Subjects that have not been recorded as dead are included as censored
[b] OS is calculated as the number of months from randomisation date to death date or last known to be alive date
[c] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio <1.0 indicates a lower average death rate and a longer overall survival for T-VEC relative to GM-CSF. 95% CI calculated from Cox regression model.
CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; KM, Kaplan-Meier; NE, non-estimable; OS, overall survival; T-VEC, talimogene laherparepvec

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

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

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

Reference: Amgen data on file[80]

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

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

Response Rates

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

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

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

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

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

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

[b] Using Fisher's Exact Test

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

Response onset

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

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

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

Reference: Amgen data on file[80] ENREF 83

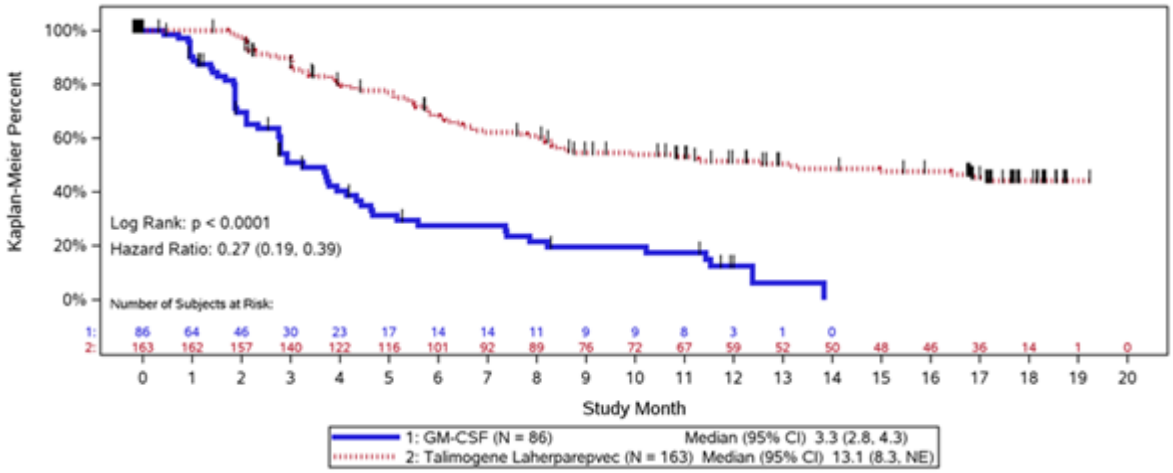
[a] The response onset is defined as the time from the date of randomization to the date of first documented evidence of response.

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

Time to Treatment Failure (TTF)

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

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



Censor indicated by vertical bar |

TTF is calculated from randomisation until the first PDr where there is no response achieved after the PDr or death if no such PDr observed. Treatment failure is censored at the last tumour assessment if the patient has not yet experienced PDr or death.

Reference: Amgen data on file[80]

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

Table 4-18: TTF per investigator assessment in patients with stage IIIB-IVM1a disease – primary data cut

	T-VEC (N=163)	GM-CSF (N=86)	Treatment difference (T-VEC/GM-CSF)
TTF per investigator assessment (months)[a]			
Median	13.1	3.3	–
95% CI	(8.3, NE)	(2.8, 4.3)	–
Hazard ratio (T-VEC/GM-CSF)[b]	–	–	0.27
95% CI	–	–	(0.19, 0.39)
p-value	–	–	<0.0001

Reference: Amgen data on file[80] _ENREF_83

[a] TTF is calculated from randomisation until the first PDr where there is no response achieved after the PDr or death if no such PDr observed

[b] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a longer average time to treatment failure for T-VEC relative to GM-CSF. 95% CI Calculated from Cox regression model

CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent-to-treat; NE, not estimable; PDr, clinically relevant disease progression; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

Duration of response

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

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

Risk of Visceral and/or Bone Metastasis

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

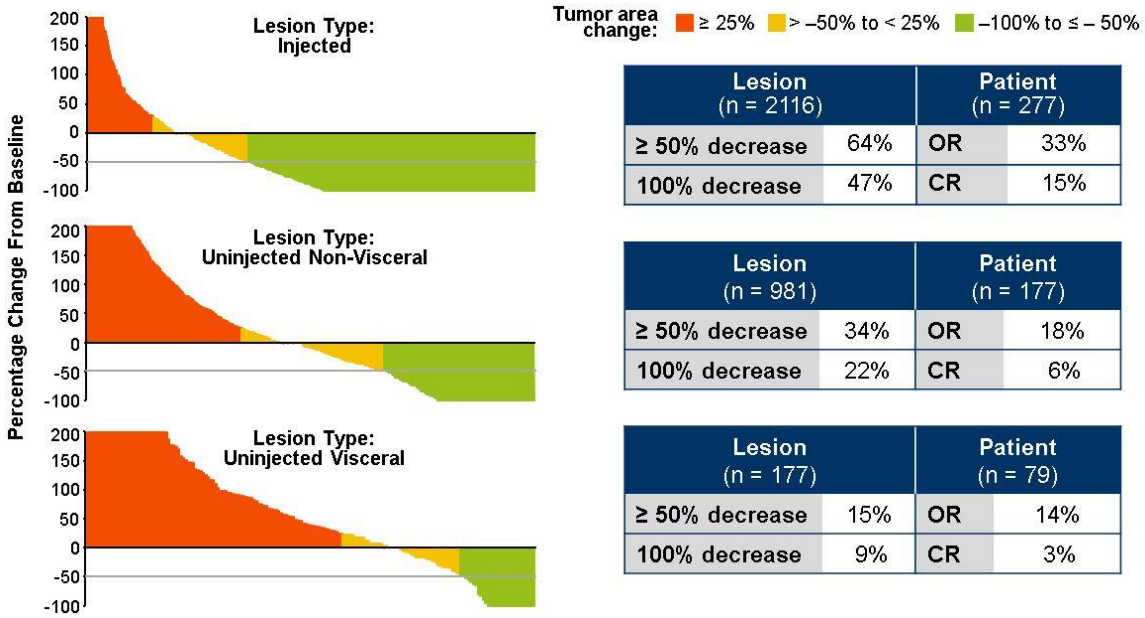
Evidence of Local and Systemic Effects of T-VEC Treatment

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

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

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

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



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

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

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

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

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

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

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

Source: Andtbacka 2014[86]

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

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

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

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

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

Reference: Amgen data on file[80]

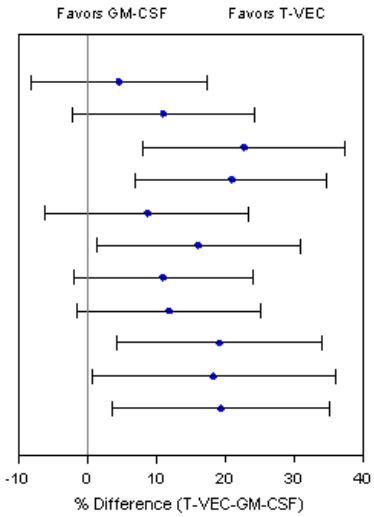
FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; GM-CSF, granulocyte–macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

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

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

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

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



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

4.9 Subgroup analysis

Not applicable.

4.10 Meta-analysis

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

4.11 Indirect and mixed treatment comparisons

Network meta-analysis feasibility assessment

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

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

Search strategy and study selection

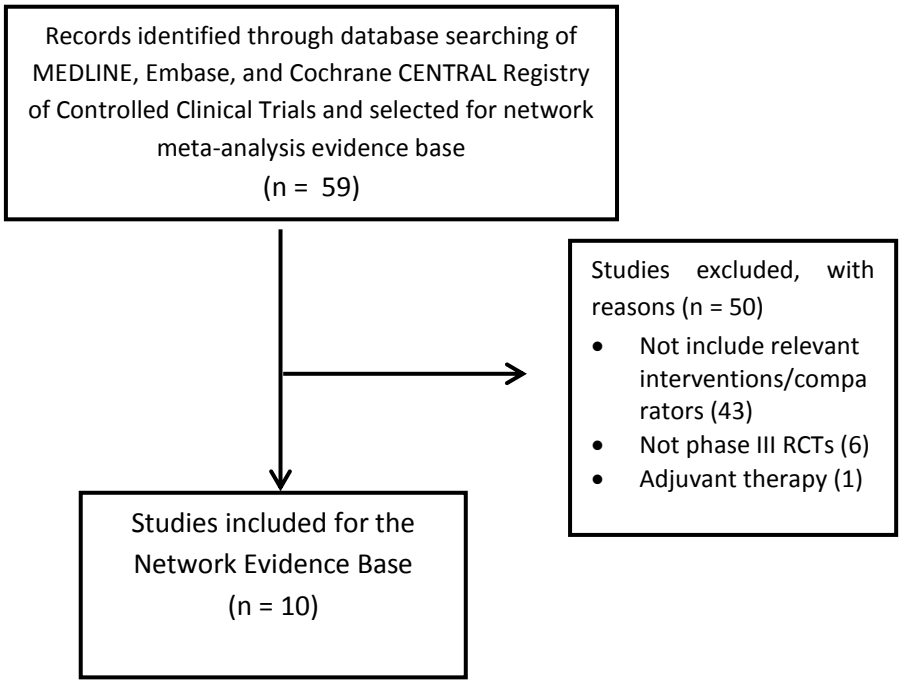
A total of 59 studies were identified in the SLR (methods and results reported in Section 4.1). However from examination of this evidence base, it was clear that T-VEC had not been evaluated against any comparator other than granulocyte-macrophage colony-stimulating factor (GM-CSF) in the OPTiM trial,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

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

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

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

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



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

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

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

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

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

Methods and results of included studies

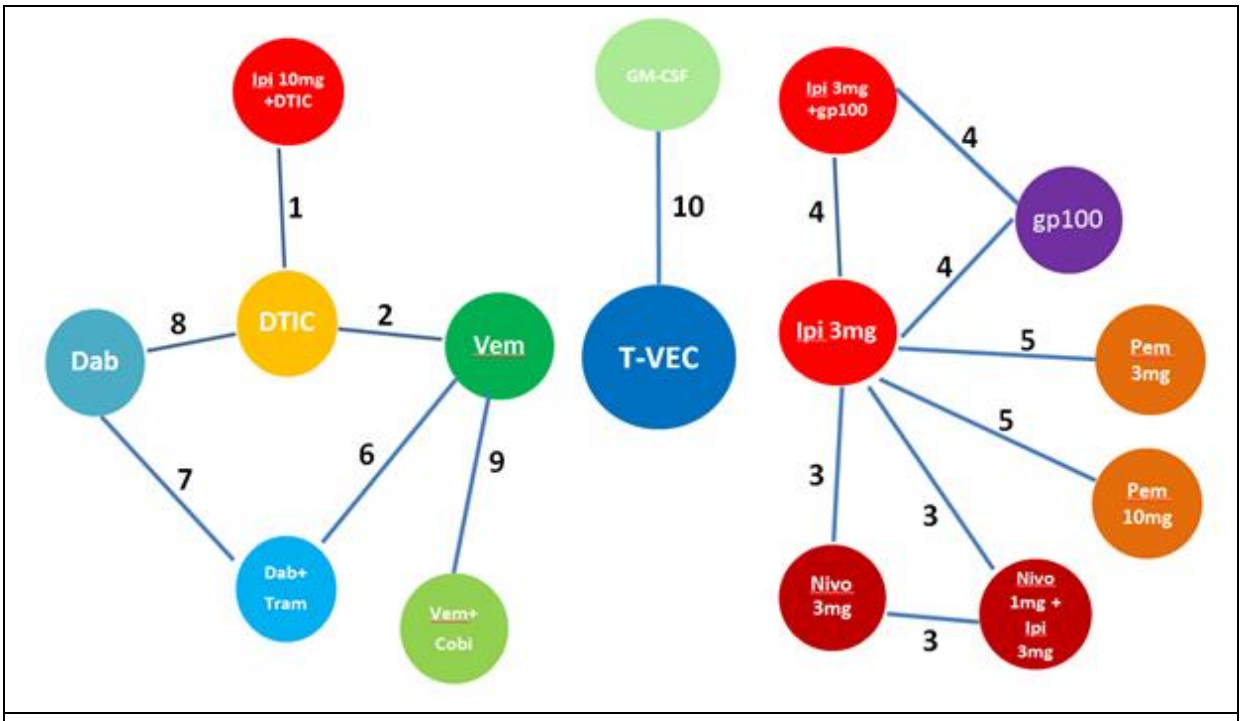
A summary of methods, outcomes, results and baseline characteristics of the included studies (excluding OPTiM) are presented in Appendix 1.4.

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

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

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

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



Numbers correspond to the study numbers in

Table 4-21

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

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

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

Assessment of alternative methods for comparative effectiveness

Evaluation of alternative methods

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

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

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

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

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

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

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

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

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

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

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

Recommendation

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

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

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

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

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

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

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

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

Search strategy and study selection

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

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

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

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

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

Methods and outcomes of included studies;

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

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

Comparison of baseline patient characteristics of included studies

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

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

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

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

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

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

The modified Korn prediction model

Development

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

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

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

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

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

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

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

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

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

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

Methods

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

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

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

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

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

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

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

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

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

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

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

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

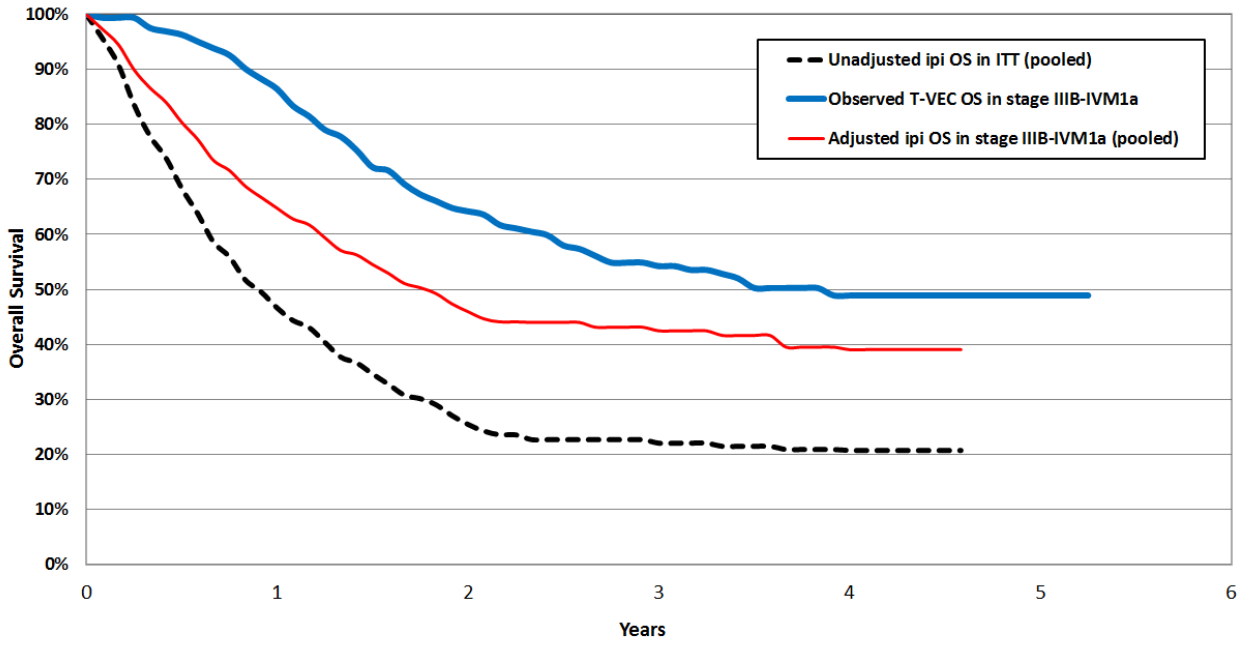
5. In case multiple curves are available for the same comparator, they are pooled by the modified Mantel-Haenszel method.

Results - median overall survival and Progression-free survival

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

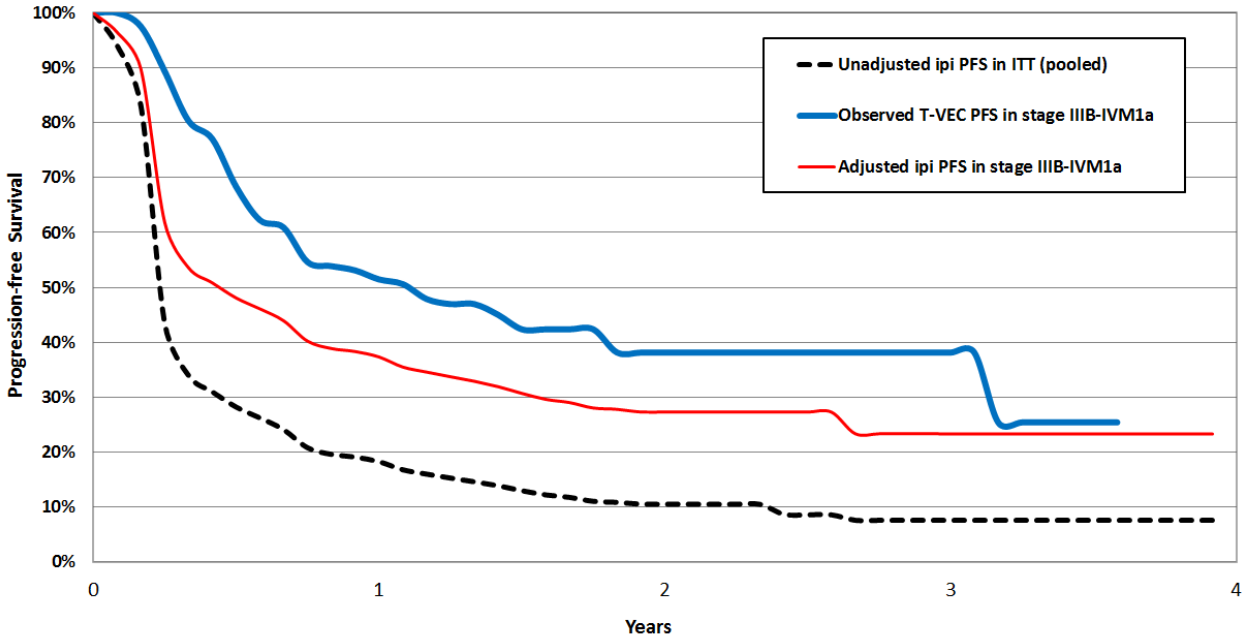
Figure 4-14 illustrates the uncertainty surrounding the adjustment with ipilimumab as characterised by the 95% prediction interval.

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



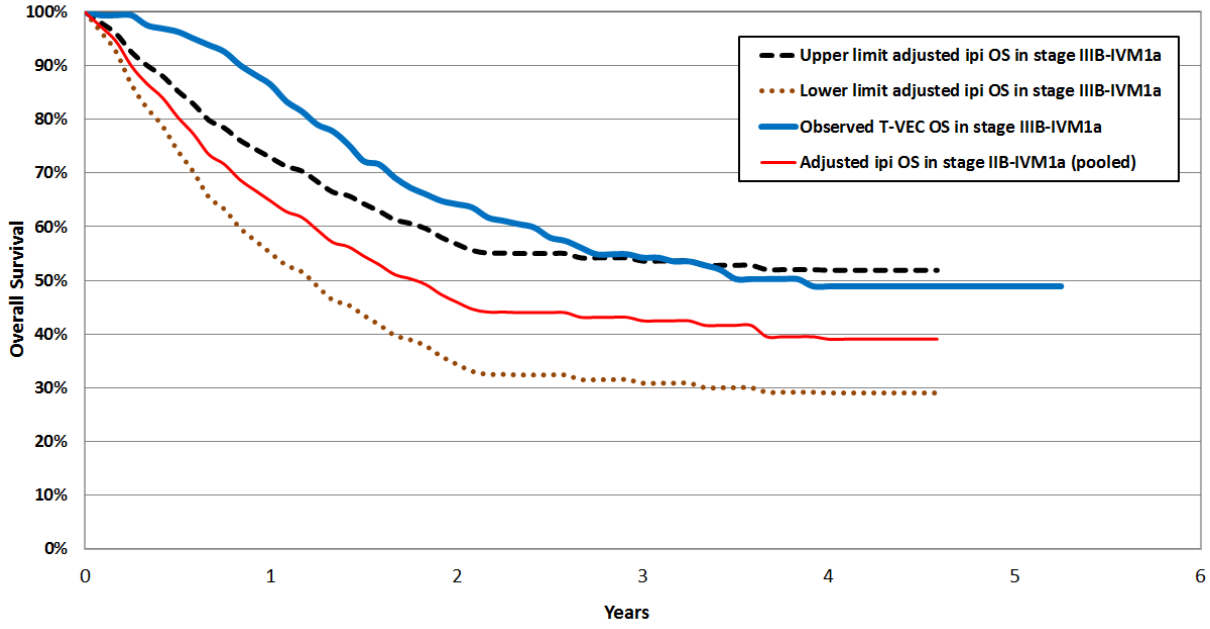
Abbreviations: OS, overall survival; ipi, ipilimumab; T-VEC, talimogene laherparepvec

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



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

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



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

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

The two-step Korn prediction model

Development

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

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

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

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

	ITT	Disease stage subgroup
Ipilimumab previously treated patients	0.64 (95% CI: 0.49-0.84)	0.47* (95% CI: 0.27-0.82) Note: 10.7% of patients had earlier stage metastatic disease
Ipilimumab previously untreated patients	0.72 (95% CI: 0.59, 0.87)	0.83** Note: <20% of patients had earlier stage metastatic disease

*Hodi provided HR 0.47 for subgroup M0, M1a, Mb
** Calculated based on the weighted average of HRs for M0 and M1a reported in Robert 2011; 95% CI is not estimated
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; RCT, randomised controlled trial

Methods

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

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

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

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

The calculated HRs are presented in Table 4-26.

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

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

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

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

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

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

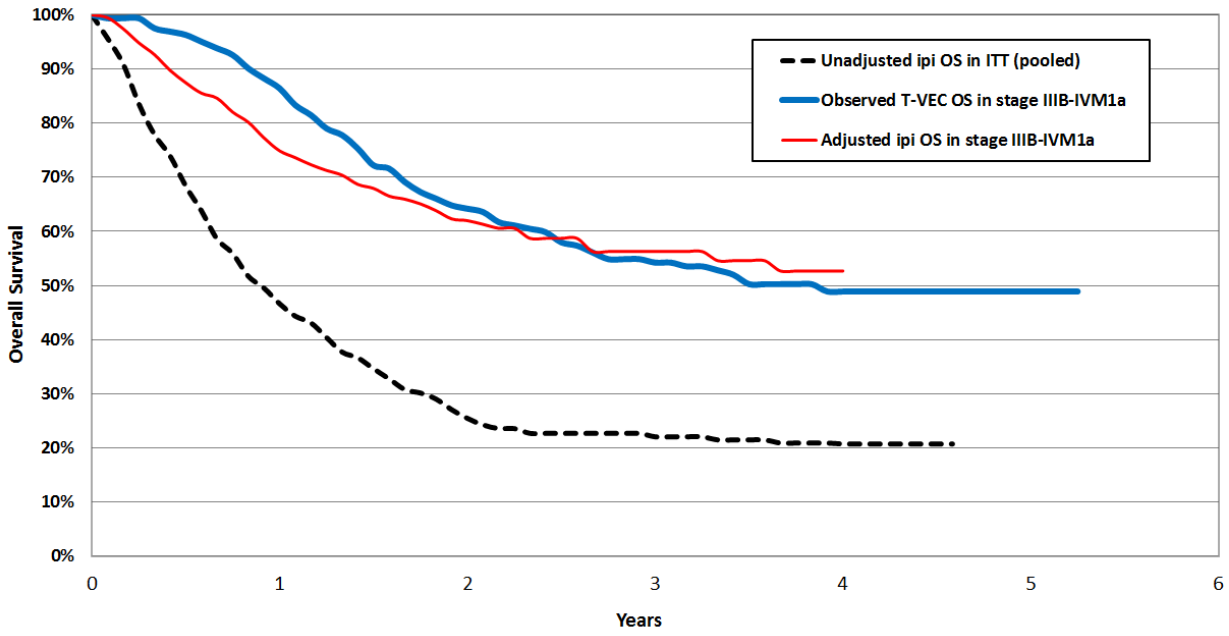
   It is noteworthy that the reported HR for ipilimumab versus gp100 in the ITT population was 0.64. It is plausible that the “true” hazard ratio for the stage IIIB-IVM1a subgroup lies in between 0.47 to 0.64. Therefore, the use of HR of 0.47 is a conservative assumption in favour of ipilimumab. The same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

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

Results

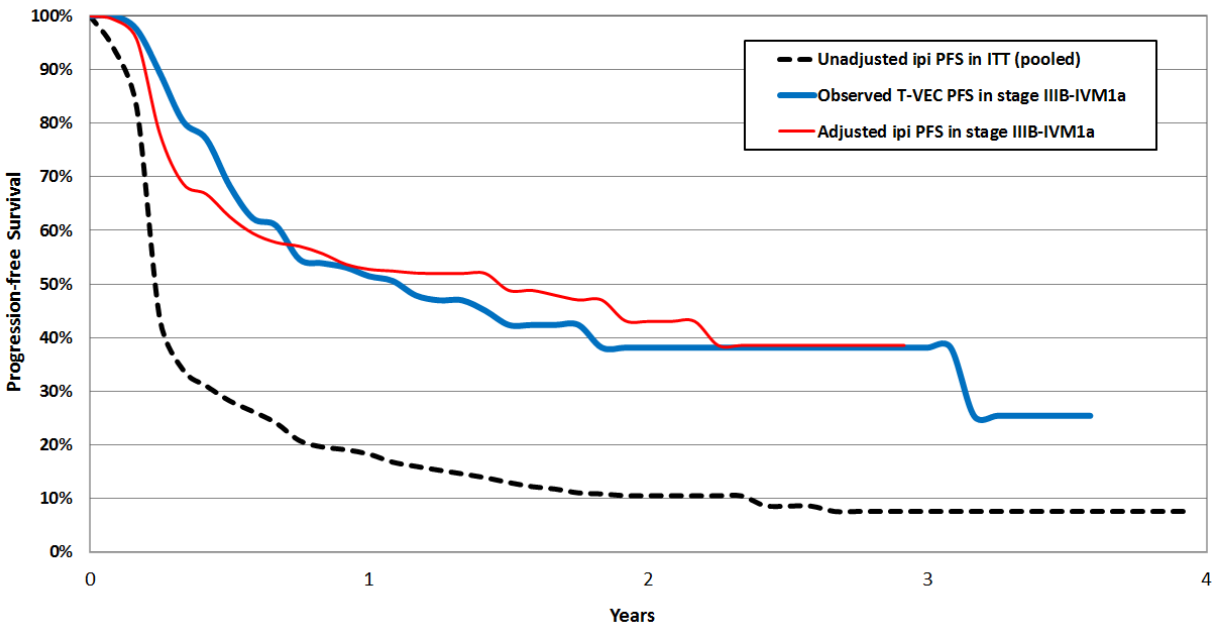
The median OS results from the meta-analysis using the two-step Korn adjustment are shown in Figure 4-15 below. The adjustment factor serves to adjust upwards the original Kaplan Meier curves such that they reflect the survival that would have been observed had ipilimumab treated a T-VEC licensed population.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

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



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

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



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

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

Limitations of methodology

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

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

Conclusion

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

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

4.12 Non-randomised and non-controlled evidence

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

List of relevant non-randomised and non-controlled evidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References: Senzer et al 2009[115]

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

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

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

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

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

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

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

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

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

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

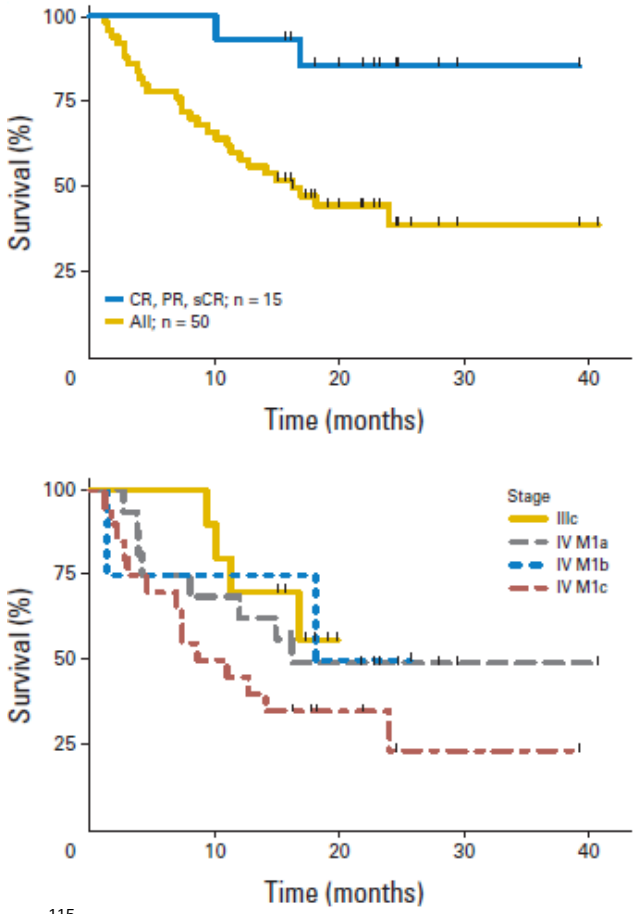
Primary endpoint: ORR

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

Secondary endpoint: OS

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

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



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

Secondary endpoint: adverse events

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

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

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

4.13 Adverse reactions

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

All AEs

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

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

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

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

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

Common treatment-emergent AEs

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

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

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

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

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

Reference: Amgen data on file[80] _ENREF_83

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

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

Common treatment-related AEs

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

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

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

Reference: Amgen data on file[80] ENREF 83

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

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

SAEs

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

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

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

Reference: Amgen data on file[80] ENREF 83

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

AEs leading to discontinuation

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

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

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

Fatal AEs

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

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

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

Summary of comparative safety data for the relevant comparators

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

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

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

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

4.14 Interpretation of clinical effectiveness and safety evidence

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

OPTiM RCT: T-VEC versus GM-CSF

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

Conclusion

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

4.15 Ongoing studies

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

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

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

5 Cost-effectiveness

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

5.1 Published cost-effectiveness studies

Identification of studies

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

Search strategy

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

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

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

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

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

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

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

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

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

Study selection

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

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

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

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

Table 5-1: Study inclusion and exclusion criteria

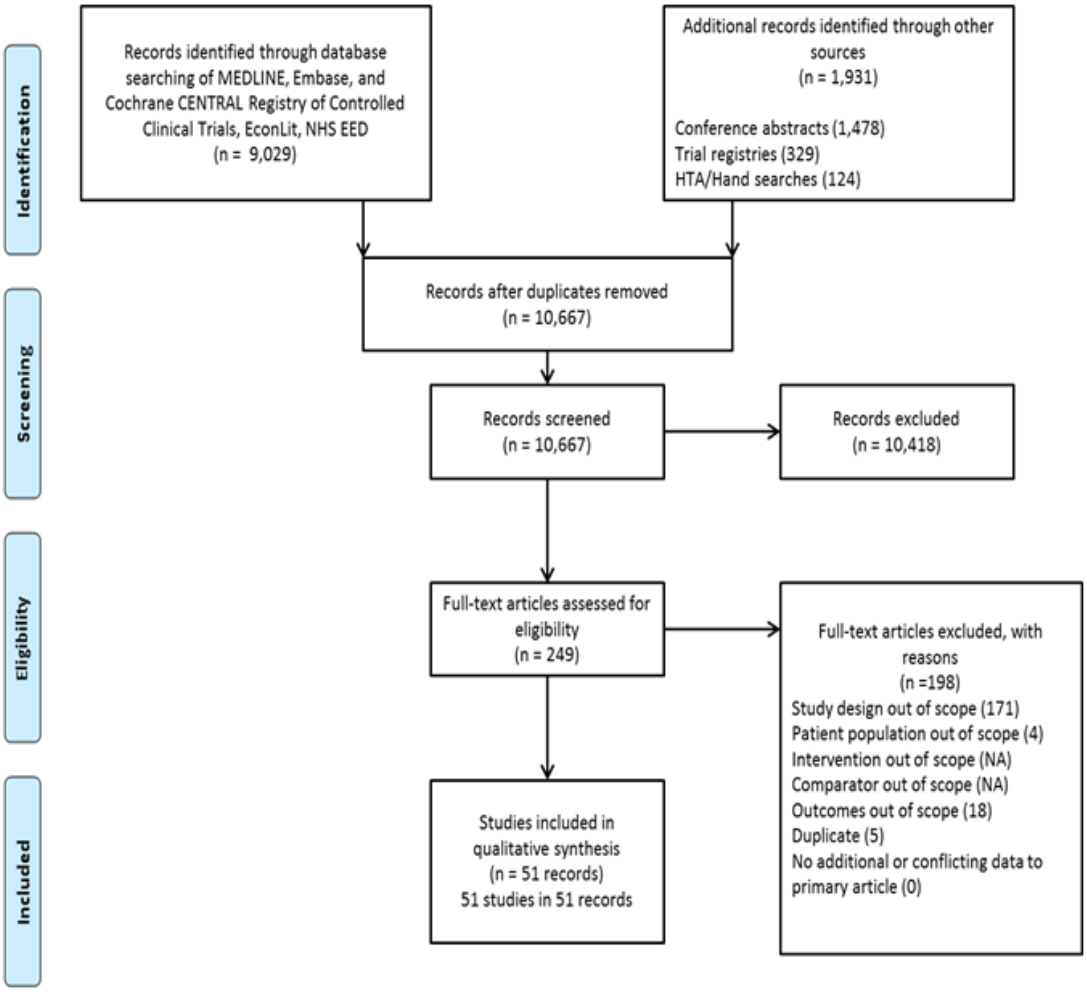
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. •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

Study selection results for economic evaluation evidence

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

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

Figure 5-1: PRISMA flow diagram for economic evidence



HTA, health technology assessment

Description of Identified studies

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

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

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

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

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

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

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

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

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

Quality assessment for each relevant cost-effectiveness study identified

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

5.2 De novo analysis

Patient population

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

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

Table 5-3: Model population base-line characteristics

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

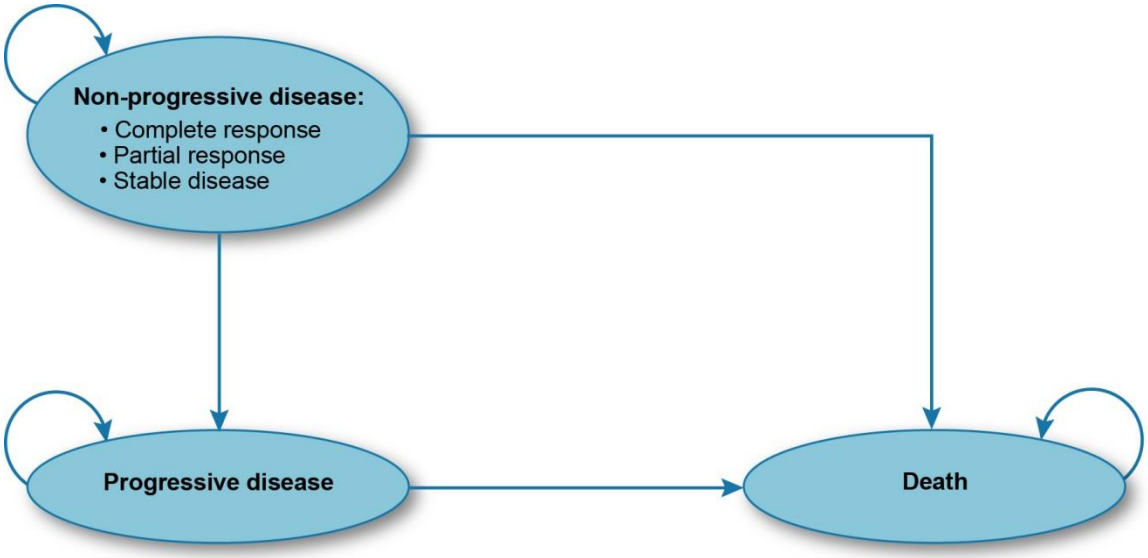
Model structure

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

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

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

Figure 5-2: Economic model structure



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

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

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

Table 5-4: Health State Definitions

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

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

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

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

Features of the de novo analysis

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

Table 5-5: Features of de novo analysis

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

Intervention technology and comparators

T-VEC dosing and treatment duration

As described in Section 4.3:

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

Ipilimumab

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

Discontinuation rules

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

5.3 Clinical parameters and variables

Describe how the clinical data were incorporated in the model

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

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

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

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

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

Overall Survival

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

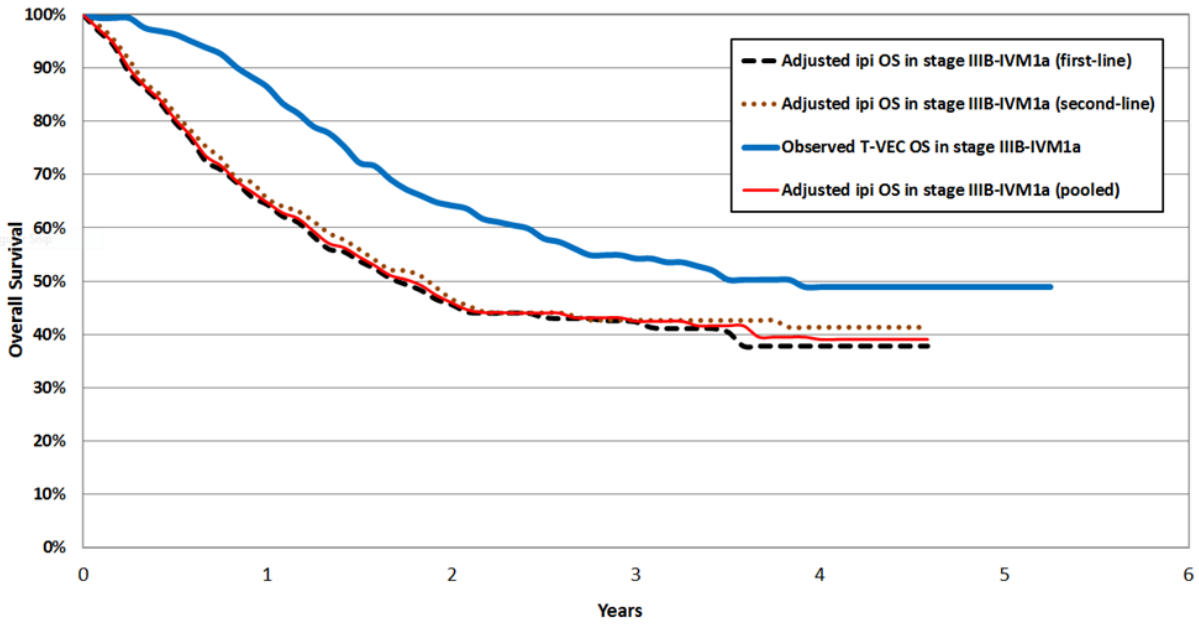
Progression free survival:

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

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

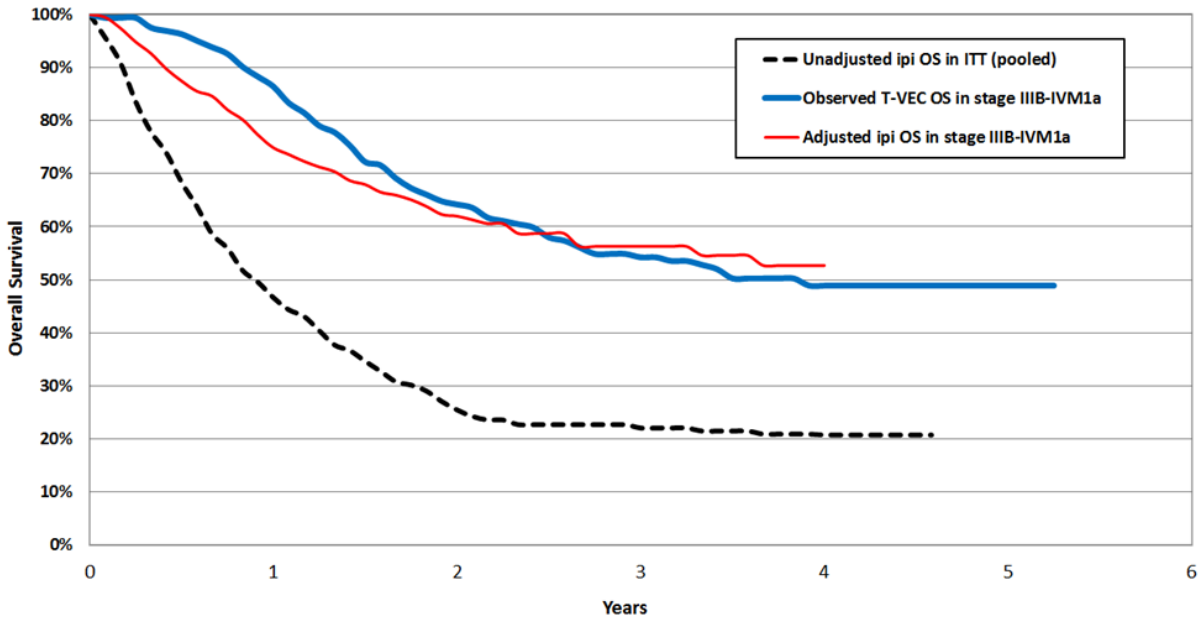
The modified Korn adjustment and two-step Korn adjustment demonstrate that there is a plausible chance that T-VEC provides an improvement in survival over ipilimumab in its anticipated licensed population (non-visceral metastatic disease) and, at worse, is no less effective. Figure 5-3 and Figure 5-4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

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



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

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



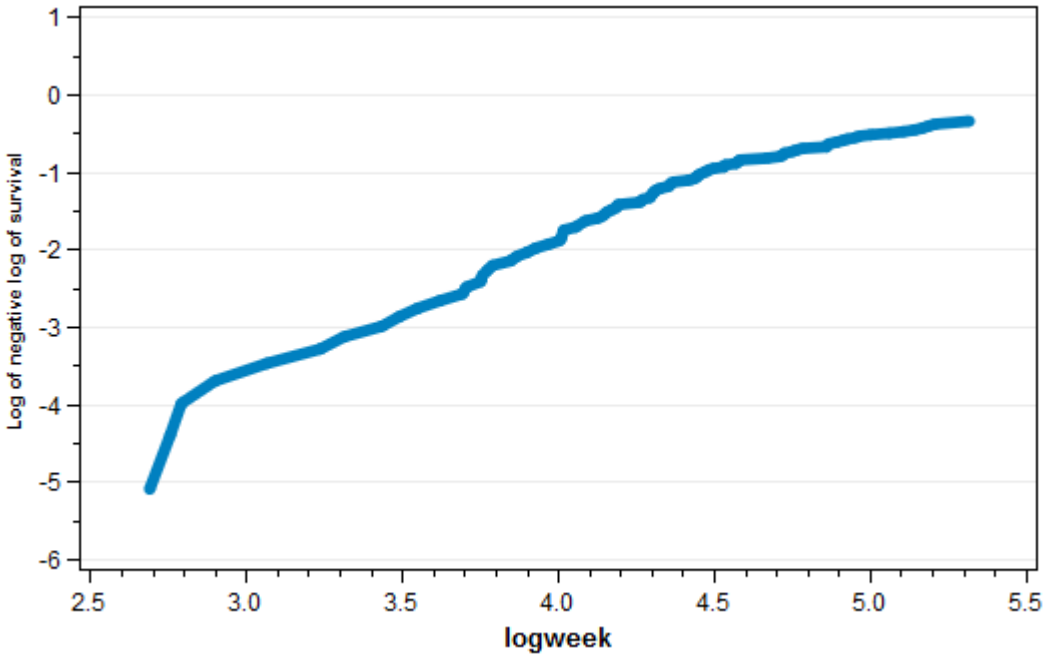
ipi, ipilimumab; ITT, intent-to-treat; OS, overall survival; T-VEC, talimogene laherparepvec

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

First part of the 3-part curve fit

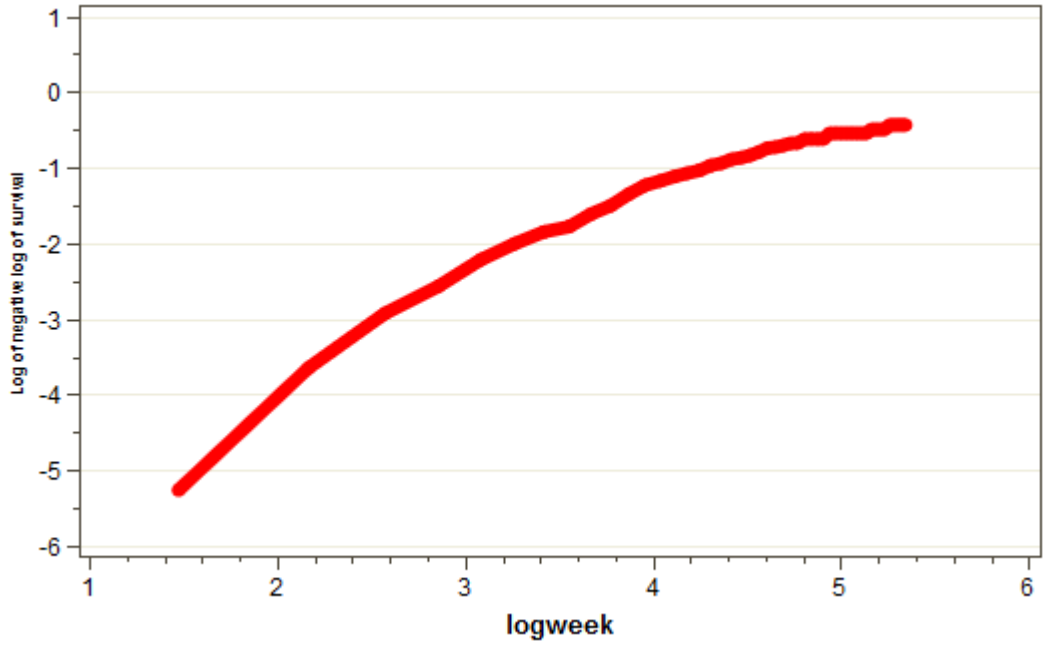
The cut point in the 3 part curve fit was determined by estimating structural changes to the Kaplan Meier curve using Chow tests[128,129]. The structural changes to the slope of the Kaplan Meier curves were tested and the time point with the most pronounced change to the slope of the Kaplan Meier curve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

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



OS, overall survival; T-VEC, talimogene laherparepvec

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



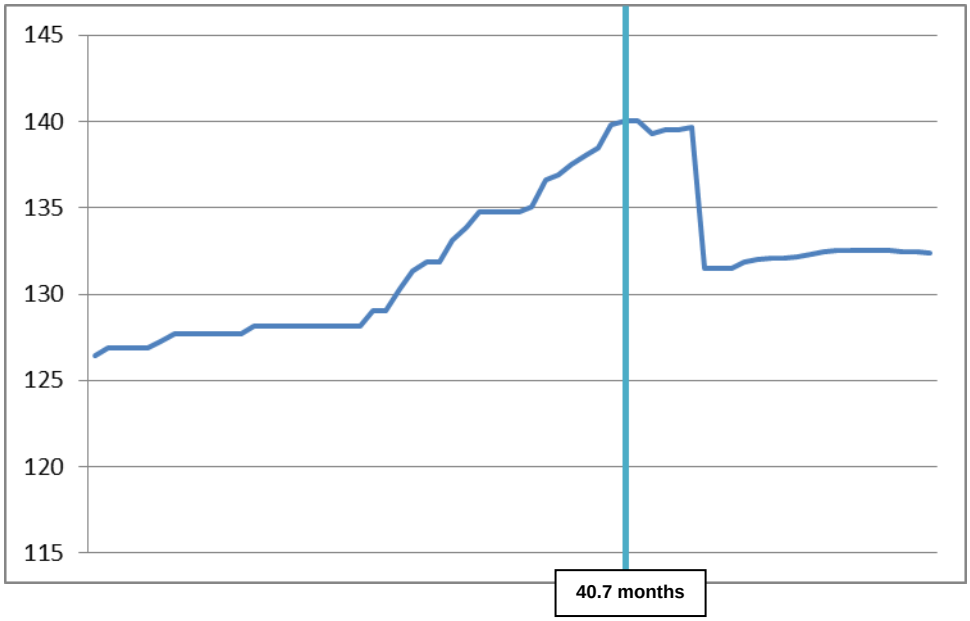
OS, overall survival

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

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

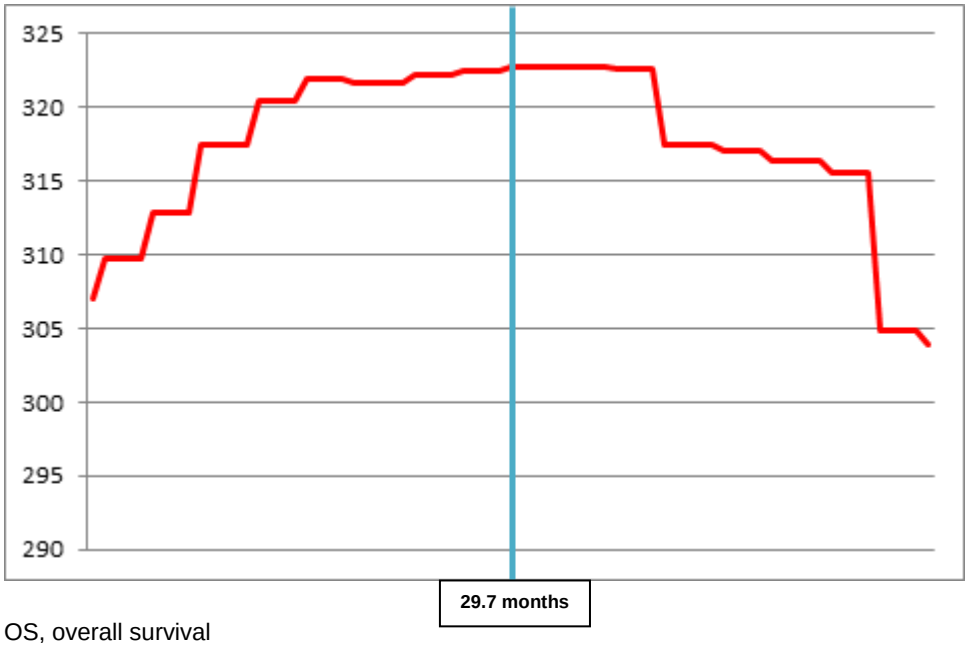
Intervention	Cut point (months)
T-VEC	**40.7**
Ipilimumab	**29.7**
OS, overall survival; T-VEC, talimogene laherparepvec	

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



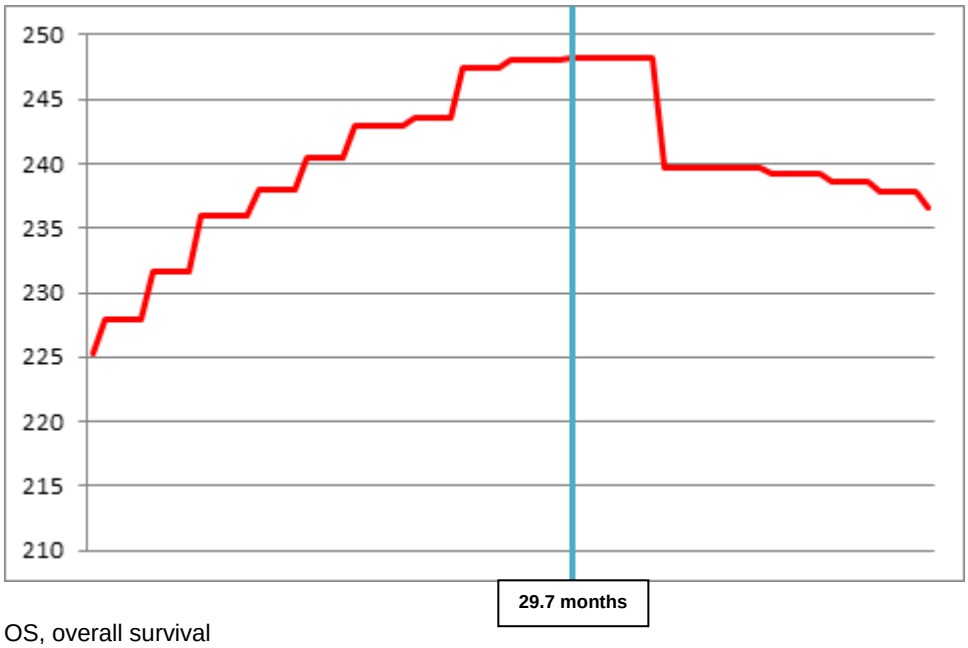
OS, overall survival; T-VEC, talimogene laherparepvec

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



OS, overall survival

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



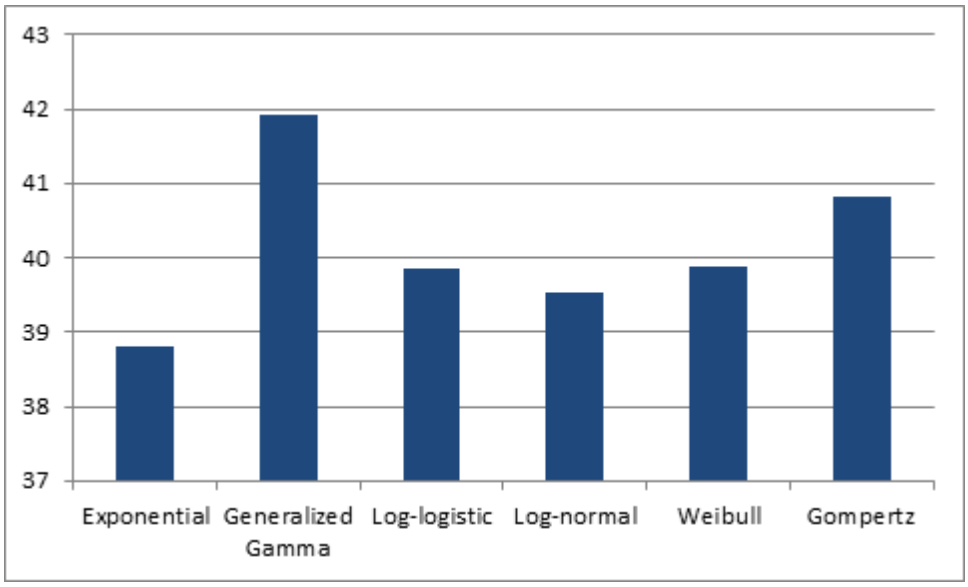
OS, overall survival

Second part of the 3-part curve fit

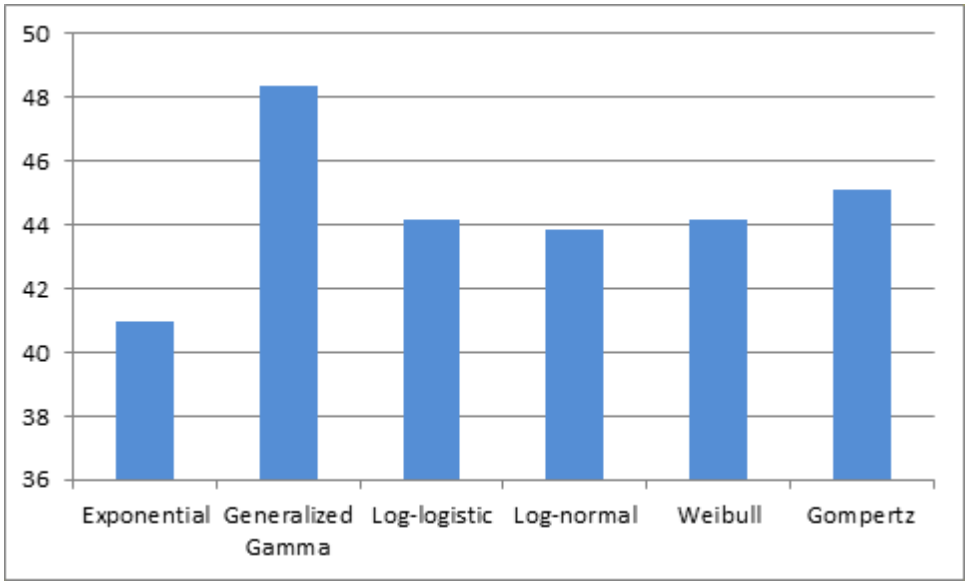
A fitted parametric curve was used from the start of the cut point to the end of the observed data from the trials (62 months and 55 months for T-VEC and ipilimumab respectively). The curve fits for the parametric curves portion were based upon goodness of fit tests, Akaike Information Criterion (AIC)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

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

AIC



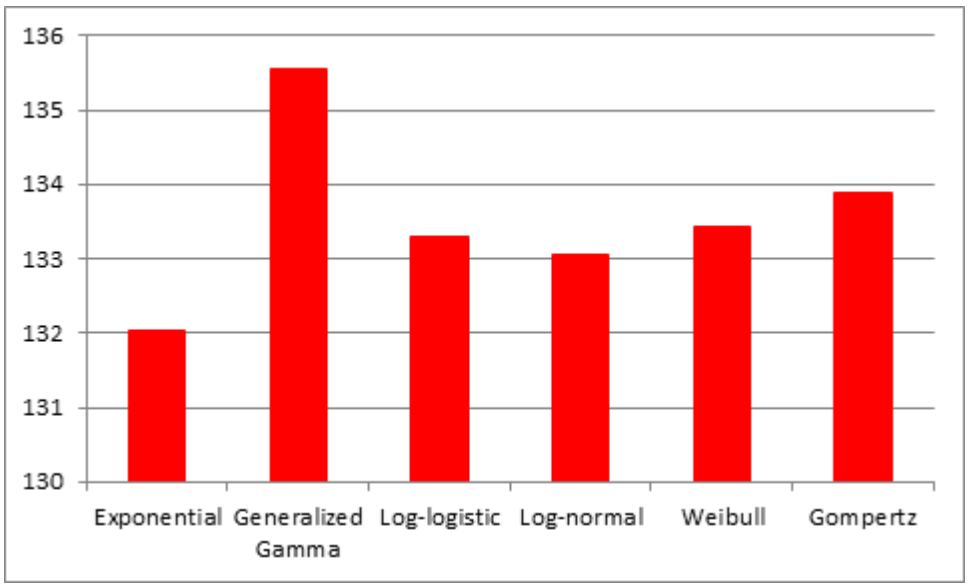
BIC



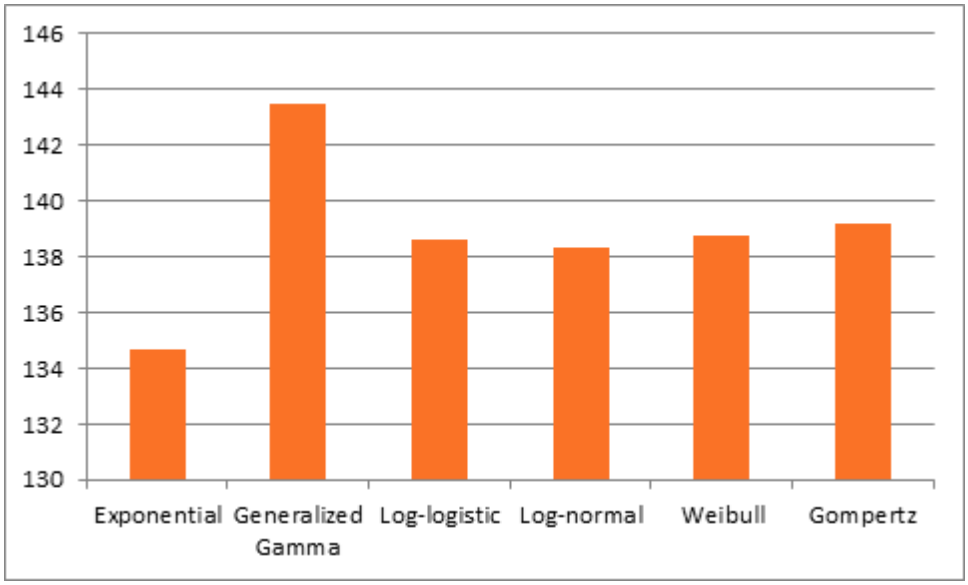
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; T-VEC, talimogene laherparepvec

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

AIC



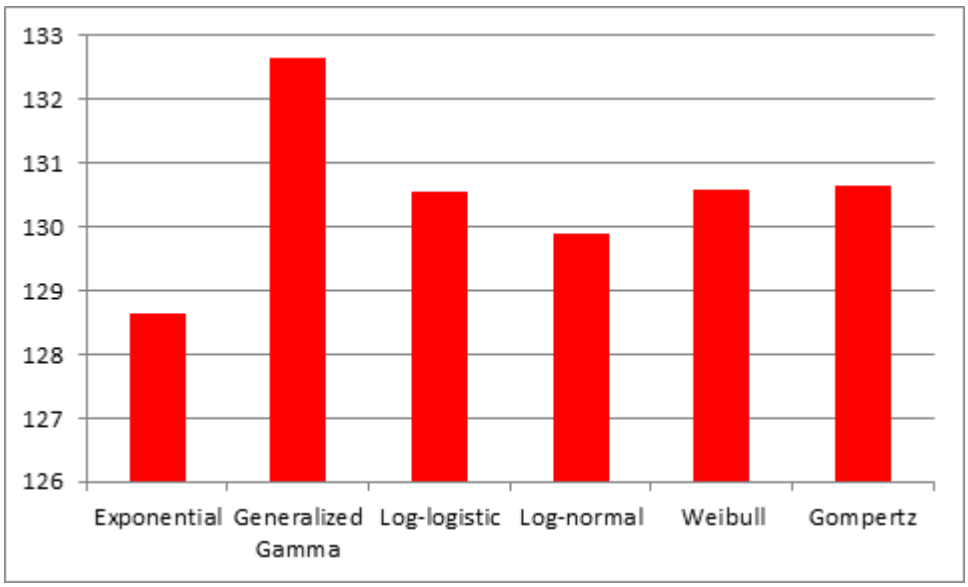
BIC



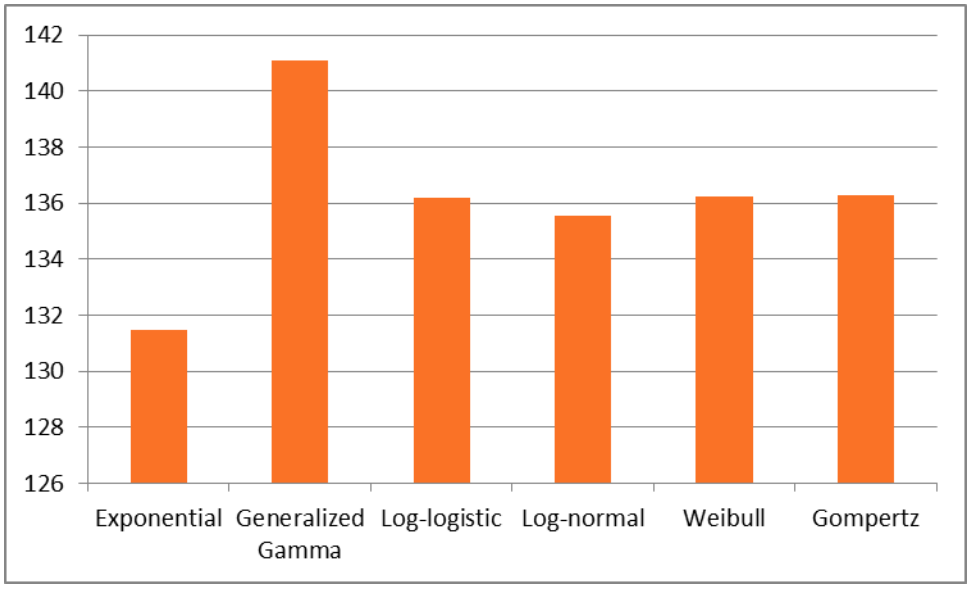
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; T-VEC, talimogene laherparepvec

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

AIC



BIC



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

Third part of the 3-part curve fit

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

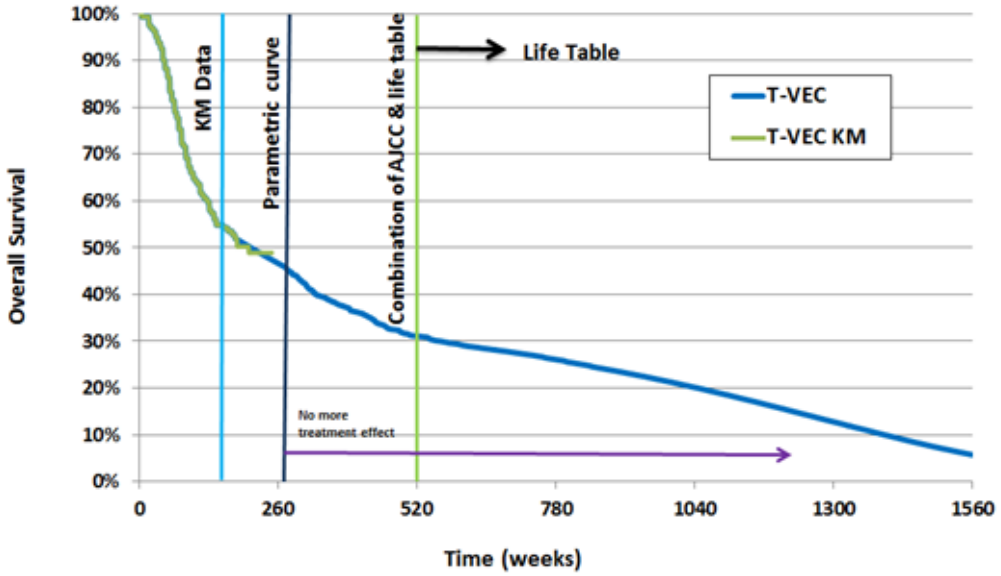
A weighted average AJCC survival curve was constructed using disease stage; i.e., AJCC by disease stage was weighted to match the distribution of disease stage at baseline in the T-VEC arm of the OPTiM trial. Mortality risk was also included from the start of the AJCC data, using data from life tables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

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

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

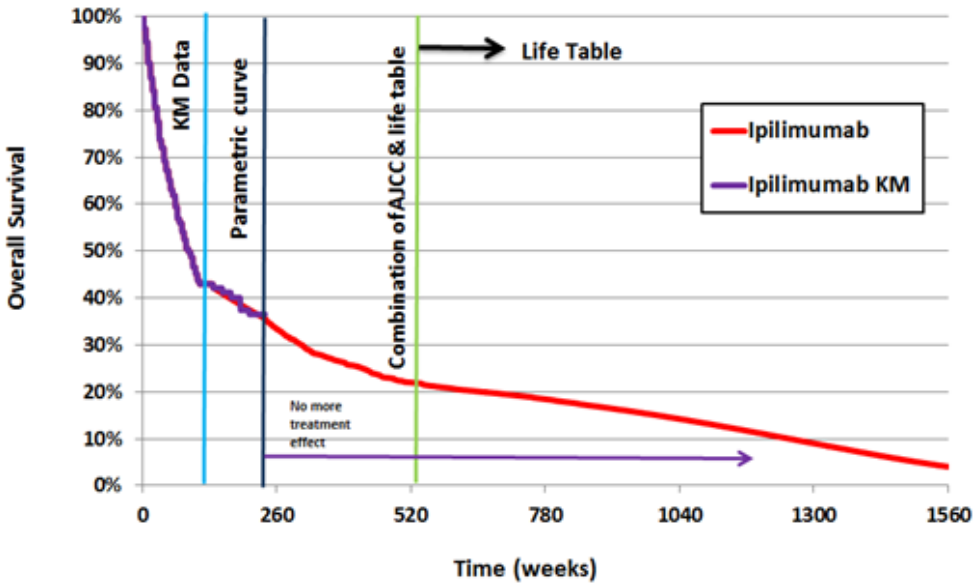
Curve part	Duration	Curve fit and parameters	Source
T-VEC			
KM data	Cycles 0-177	N/A	OPTiM[79]
Parametric curve	Cycles 178-269	Exponential Intercept: 5.1359 Scale: 1.0000	Curve fitted to survival of patients alive at 177 weeks
Registry data hazards and life table, then life table alone	Cycles 270+	N/A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

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



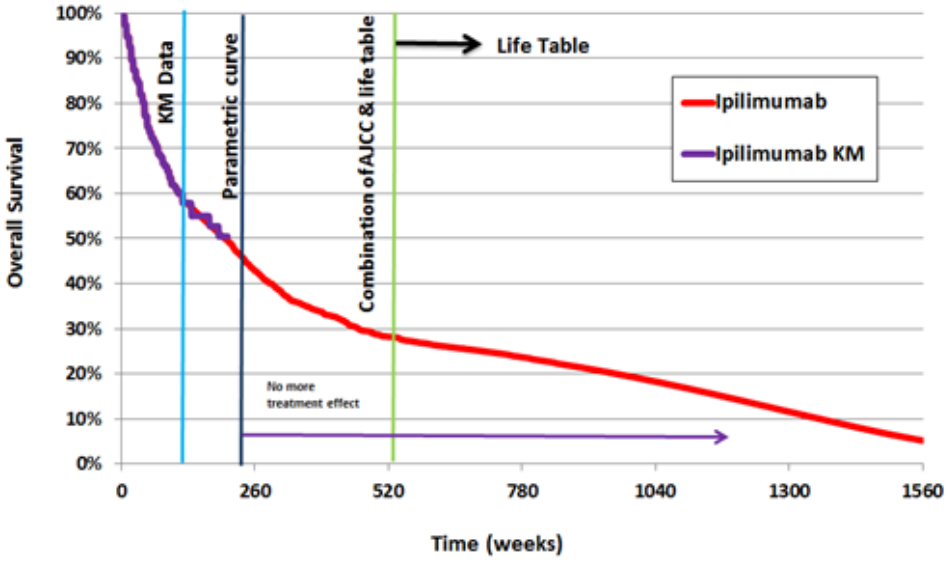
AJCC; American Joint Committee on Cancer; KM, Kaplan-Meier; OS, overall survival; T-VEC, talimogene laherparepvec

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



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

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



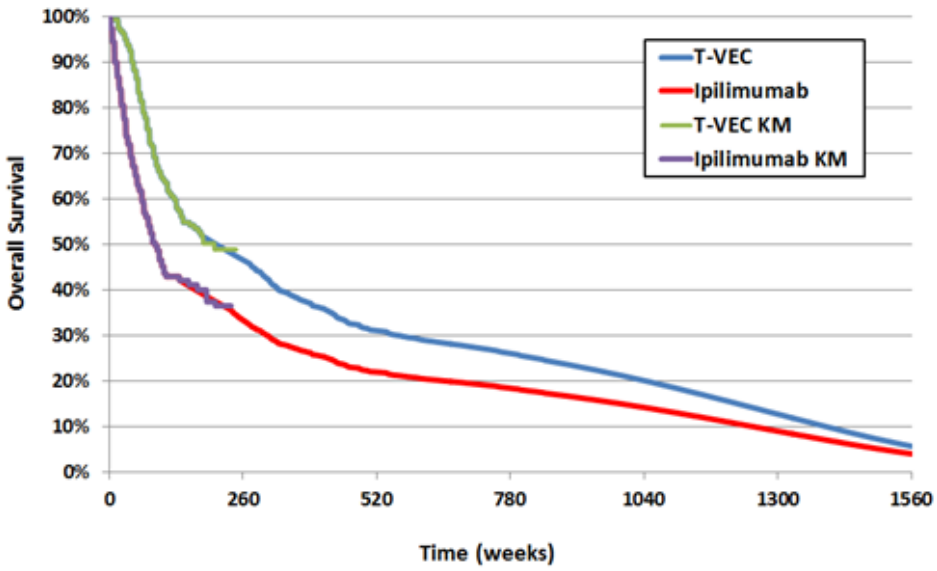
AJCC; American Joint Committee on Cancer; KM, Kaplan-Meier; OS, overall survival

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

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

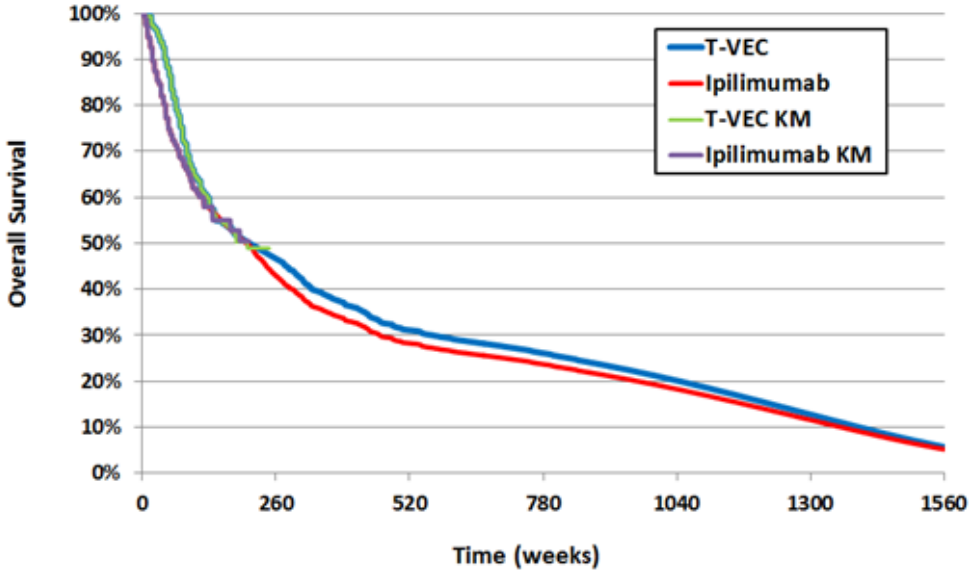
The two-step Korn adjustment, in contrast, not only assumes the presence of an interaction effect but also assigns the best possible magnitude of this effect to ipilimumab. Consequently, the resulting mean OS gain for T-VEC of 0.5 life years (6.66 years and 4.90 years for T-VEC and ipilimumab respectively,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

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



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

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



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

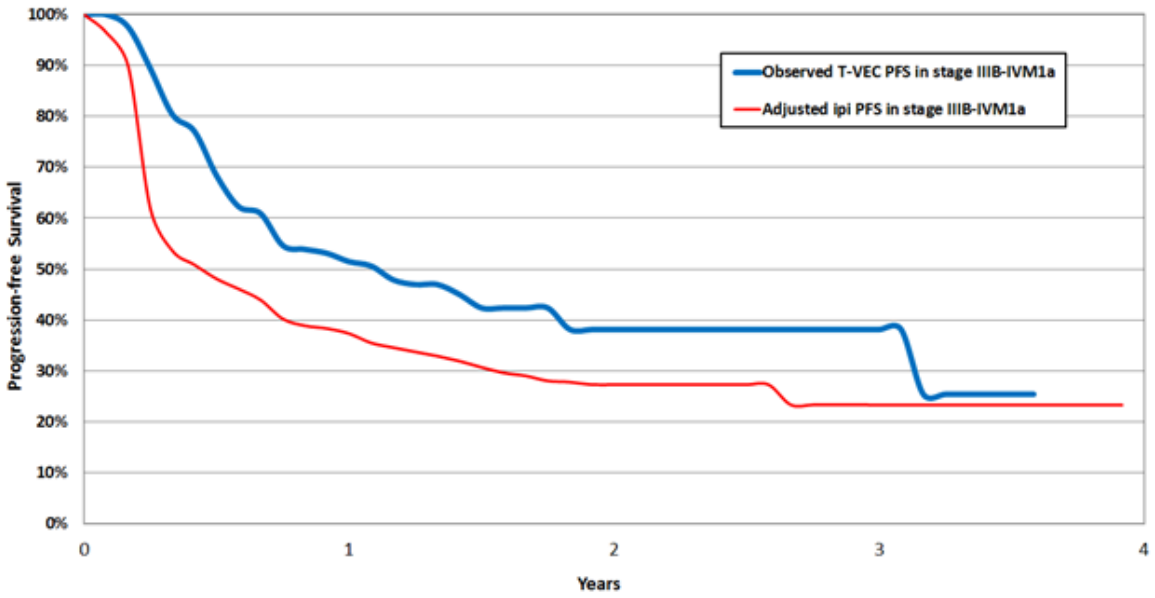
Modelling progression free survival for T-VEC and Ipilimumab

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

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

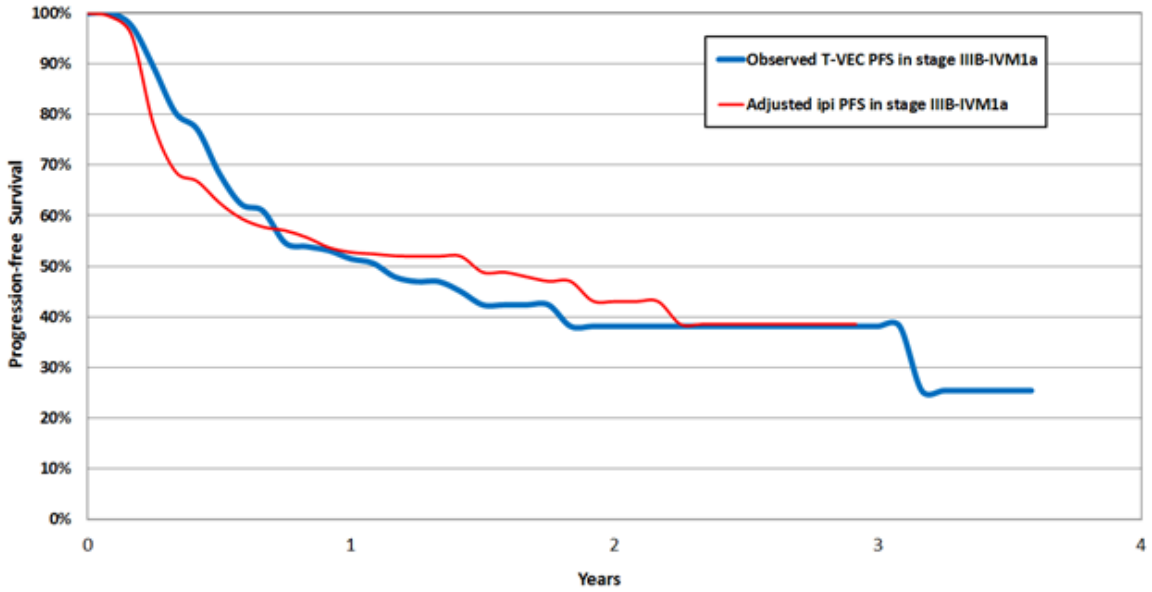
Figure 5-18 and Figure 5-19 below present the adjusted Kaplan Meier PFS, based on the modified Korn adjustment and the two-step Korn adjustment for ipilimumab in patients with stage IIIB-IVM1a disease.

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



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

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

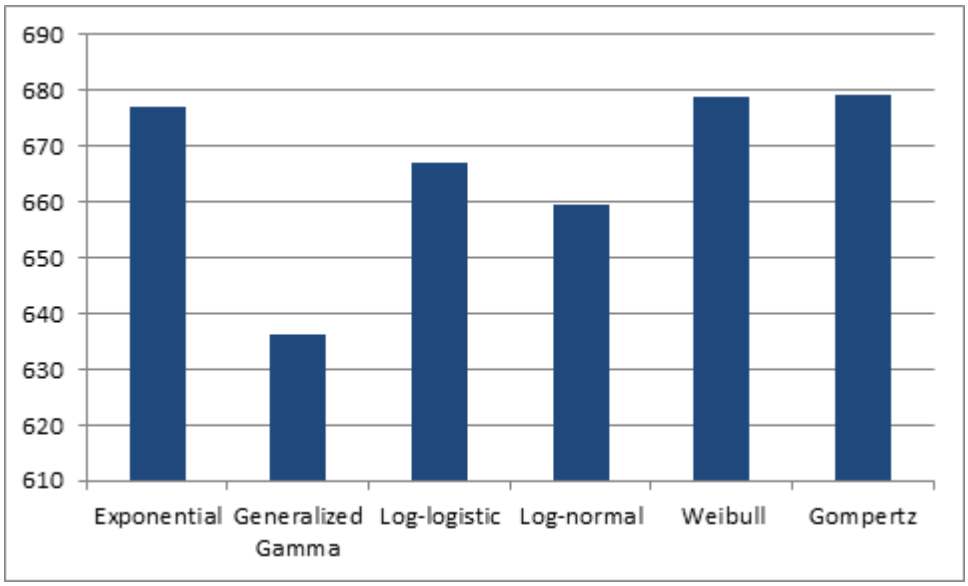


PFS, progression-free survival; T-VEC, talimogene laherparepvec

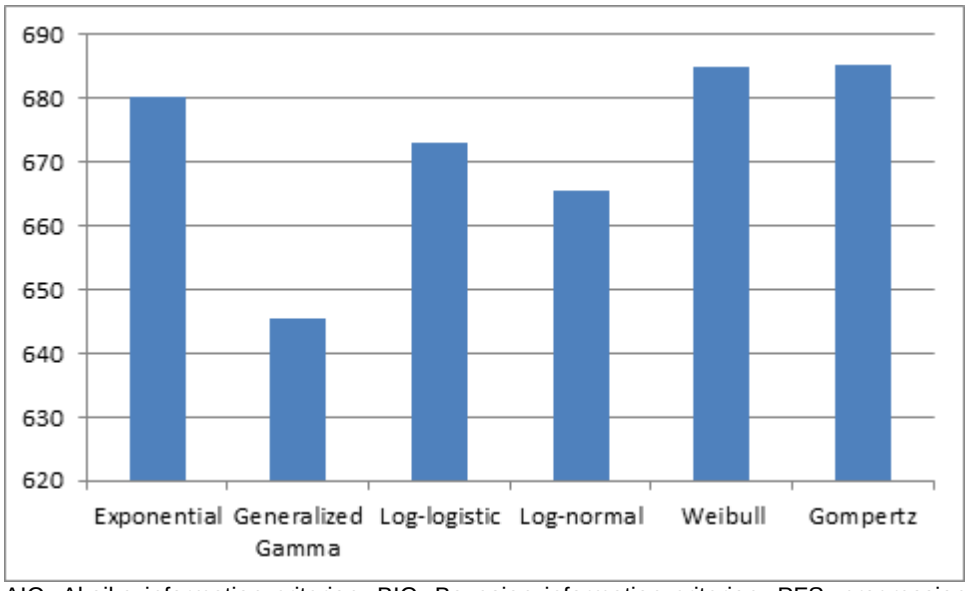
A fitted parametric curve was used to extrapolate PFS. The curve fits for the parametric curves were based upon goodness of fit tests, AIC and BIC (Figure 5-20 and Figure 5-21). Based on visual inspection as well as goodness of fit tests, a generalised gamma curve was used for both T-VEC and ipilimumab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

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

AIC



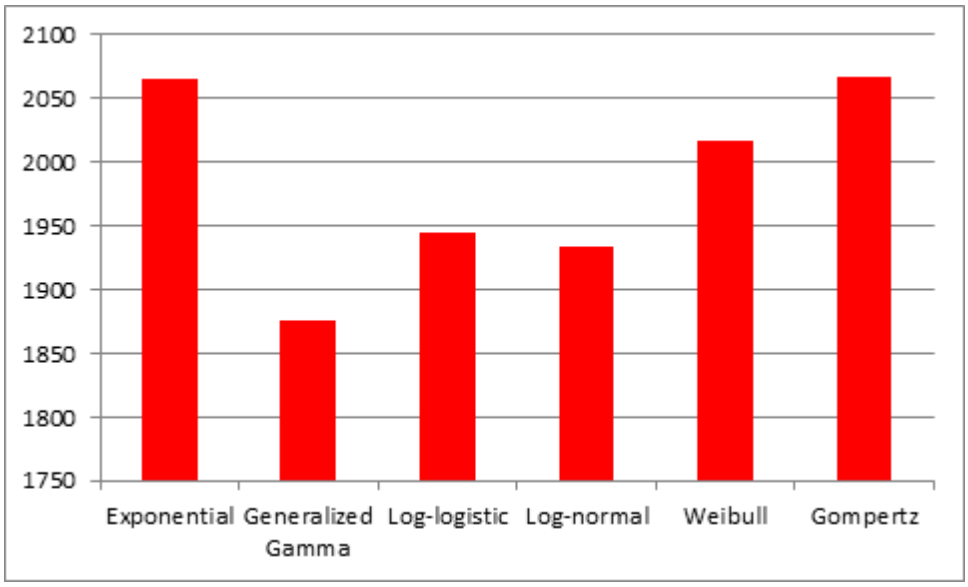
BIC



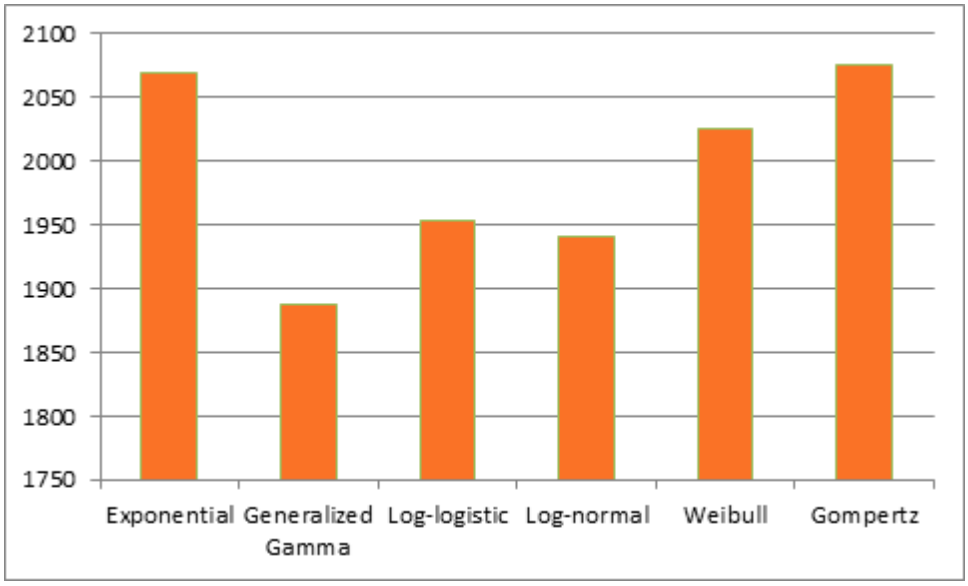
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; T-VEC, talimogene laherparepvec

Figure 5-21: AIC and BIC goodness of fit statistics for PFS curve fits for ipilimumab based on modified Korn adjustment

AIC



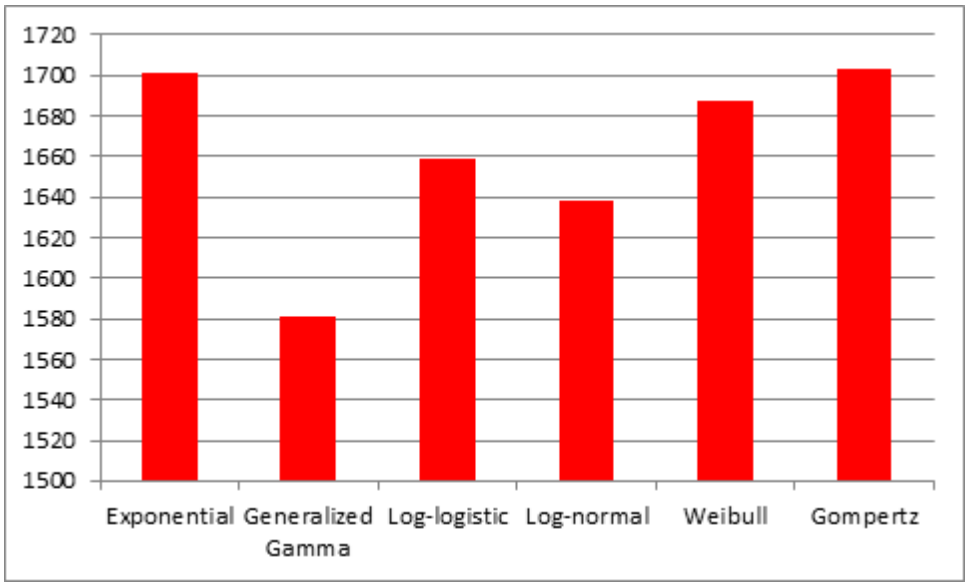
BIC



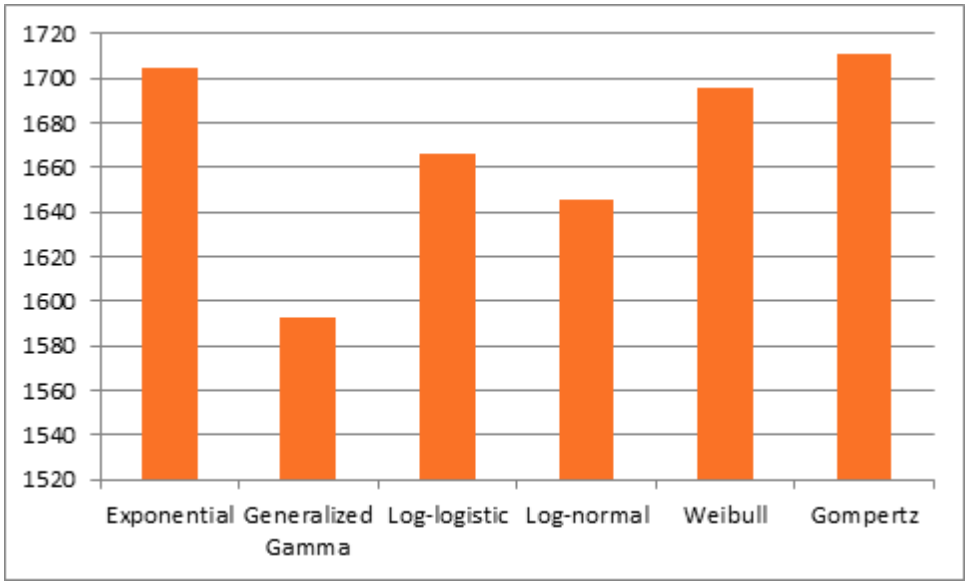
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival

Figure 5-22: AIC and BIC goodness of fit statistics for PFS curve fits for ipilimumab based on two-step Korn adjustment

AIC



BIC



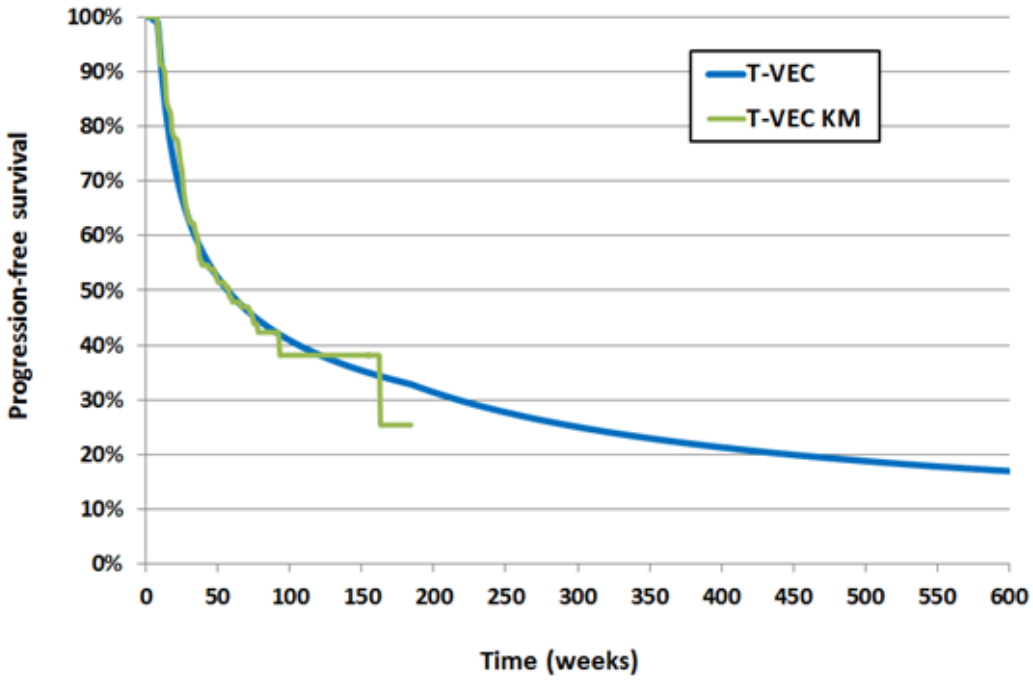
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival

The base case curve is described in Table 5-8 below and the estimated PFS curves are displayed in Figure 5-23 to Figure 5-25.

Table 5-8: T-VEC and ipilimumab base case PFS curve using regression

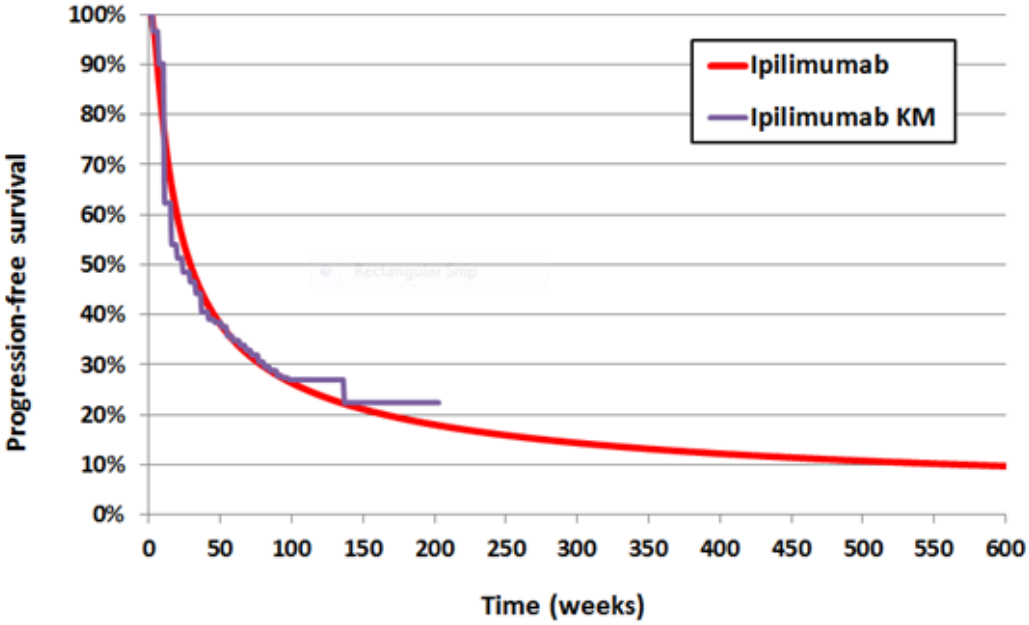
Curve part	Duration	Curve fit and parameters	Source
T-VEC			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 0.85010 Scale: 0.46000 Shape: -6.10950	Curve fitted to PFS of all patients
Ipilimumab (Based on Modified Korn adjustment)			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 1.20460 Scale: 1.26720 Shape: -1.39870	Curve fitted to PFS of all patients
Ipilimumab (Based on two-step Korn adjustment)			
Parametric curve	Cycles 0+	Generalised Gamma Intercept: 1.44460 Scale: 1.27410 Shape: -2.05300	Curve fitted to PFS of all patients
Abbreviations: PFS, progression free survival; T-VEC, talimogene laherparepvec			

Figure 5-23: One curve fit for T-VEC PFS



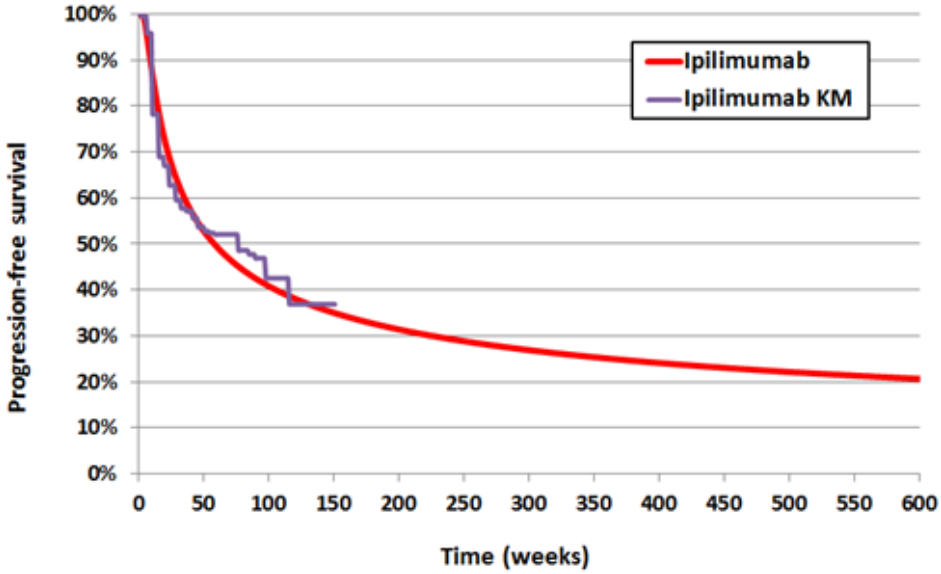
KM, Kaplan Meier; PFS, progression free survival; T-VEC, talimogene laherparepvec

Figure 5-24: One curve fit for ipilimumab PFS (based on modified Korn adjustment)



KM, Kaplan Meier; PFS, progression free survival

Figure 5-25: One curve fit for ipilimumab PFS (based on two-step Korn adjustment)



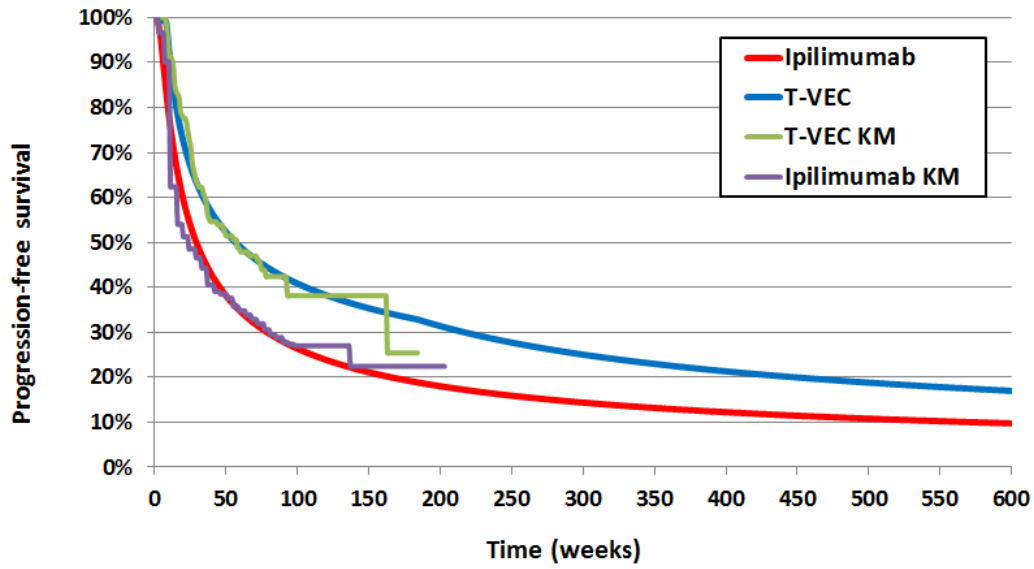
KM, Kaplan Meier; PFS, progression free survival

The final estimated PFS predictions for T-VEC and ipilimumab using the modified Korn adjustment is shown in Figure 5-26 below. Similarly, Figure 5-27 shows the same based on the two-step Korn adjustment.

As discussed previously, the paucity of data for ipilimumab in patients with non-visceral metastatic disease, presents genuine uncertainty around the critical clinical issue of the treatment effect in non-visceral metastatic disease. The modified Korn adjustment adjusts for the baseline prognostic variables and assumes that there is no interaction with treatment for patients with non-visceral metastatic disease except that beyond disease stage prognosis.

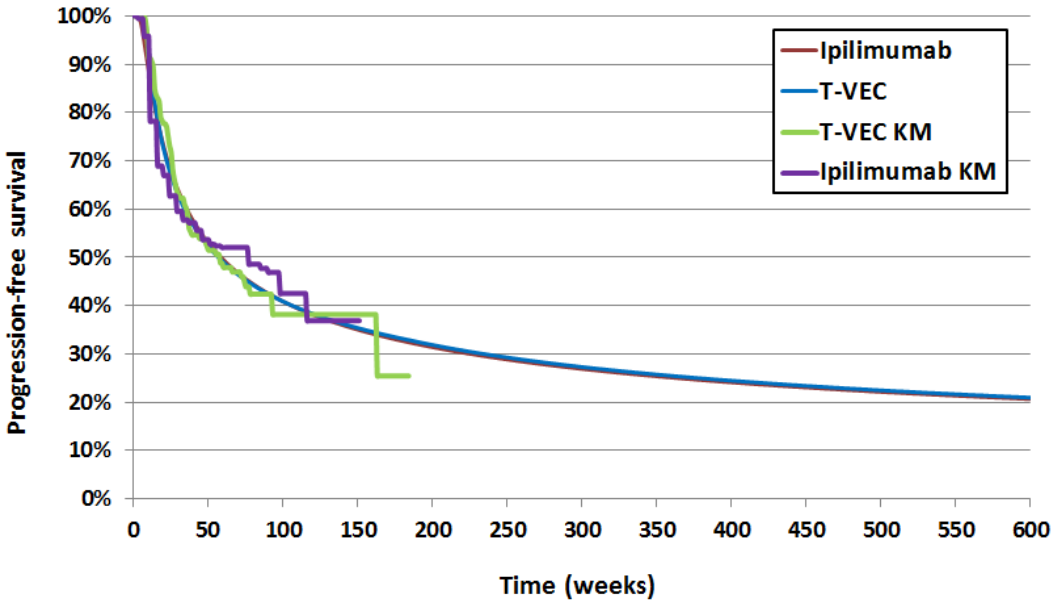
This may be deemed to be the most favourable scenario of the PFS gain of T-VEC versus ipilimumab (Figure 5-26) of 1.55 years (4.22 years and 2.67 years for T-VEC and ipilimumab respectively,. The two-step Korn adjustment (Figure 5-27), in contrast not only assumes the presence of an interaction effect but also assigns the best possible magnitude of this effect to ipilimumab. Consequently, the resulting mean PFS gain for T-VEC of 0.08 years (4.69 years and 4.62 years for T-VEC and ipilimumab respectively) may be deemed to be the worse-case scenario for T-VEC.

Figure 5-26: Comparative PFS for T-VEC and ipilimumab (based on Modified Korn adjustment)



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

Figure 5-27: Comparative PFS for T-VEC and ipilimumab (based on two-step Korn adjustment)



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

Calculation of transition probabilities from the clinical data

Transition probabilities are not applicable given the structure of the model, however as described in Section 5.3, the model was developed by fitting survival curves to the observed trial data for OS and PFS, and the proportion of patients in each health state was determined as follows:

- Non-progressive/pre-progressive disease health state was equal to whichever was lower of the OS or PFS curve in each cycle. This approach resolved any conflicts in instances where the OS curve estimated a lower probability of survival than the PFS curve.
- Progressive disease health state was equal to the difference between the OS and PFS curves in each cycle
- Dead health was equal to the complement of the OS curve in each cycle

Evidence that (transition) probabilities may change over time

A detailed description of the extrapolation methods was previously provided above.

Input from clinical experts

The clinical parameters used in the economic model were derived from the available evidence; three clinical experts in the field of melanoma and a health economist were consulted to discuss the clinical plausibility of the indirect comparison of T-VEC and the relevant comparators, the approach to survival modelling and the plausibility of the survival estimates generated from the clinical data.

The selection of the clinical experts was based upon their availability and all had experience of T-VEC and the comparators defined in the decision problem either in a clinical trial or through routine clinical practice. The clinicians practiced in three different geographical locations across the UK and received an honorarium for their review which was conducted via individual telephone interviews.

There was general agreement that the efficacy of T-VEC versus GM-CSF in the anticipated license population was clinically meaningful and significant. There was also acknowledgement of the challenges of performing an indirect comparison (given broken networks and heterogeneity of patient populations) to estimate the survival gain between T-VEC versus ipilimumab and consequently the Korn methodology was deemed to be an appropriate method given these challenges.

5.4 Measurement and valuation of health effects

Melanoma can have a significant impact on the HRQoL of patients, with many patients facing physical, emotional and psychological challenges. Additionally, many treatments for advanced melanoma are associated with significant toxicity resulting in symptoms such as diarrhoea, nausea, stomatitis, hair loss and flu-like syndrome that can also have an impact on a patient's quality of life[130].

Although patients with metastatic disease may have a high level of functioning at diagnosis, rapid progression of disease leads to a decline in almost all of the major physical and social functional domains[33]. Long term survival due to clinical improvement is expected to result in an increase in utility or the utility remaining the same; however for patients who do not

become long-term survivors, the quality of life has been shown to decrease with a large reduction the quality of life in the month prior to death[131,132].

Health-related quality-of-life data from clinical trials

Summary of clinical data

As described in Section 4.8, quality of life was assessed in OPTiM using the FACT-BRM and patients were required to complete the questionnaire prior to any treatment-related study procedures (including administration of investigational product) on day 1 of each treatment cycle and at the end of trial visit.

Baseline questionnaires were completed by 95.7% of patients in the T-VEC arm and 82.6% in the GM-CSF arm, with completion rates in subsequent cycles lower in both arms of the trial. Additionally, a more rapid decline in the questionnaire completion rates was observed for patients in the GM-CSF arm compared to those in the T-VEC arm which was most likely related to the differences in the rate of treatment discontinuation, disease progression and death in the GM-CSF arm (Section 4.8; Table 4-19).

Analysis of the FACT-BRM showed that more patients treated with T-VEC than those treated with GM-CSF had an improvement in all 11 subscales of the questionnaire (Figure 4-9) and a statistically significant difference in favour of T-VEC was observed in 6 of the measures (Emotional Well-Being, Functional Well-Being, Social/Family Well-Being, overall QoL, pain, and ability to work).

Amgen time trade-off study

A separate Amgen sponsored time-trade off (TTO) utility study was conducted to elicit the preferences of members of the UK general public for health states associated with advanced melanoma (Appendix 1.7). The health states assessed in the study were consistent with the patient outcomes in the OPTiM trial and the health states in the economic model (Section 5.2). Only AEs with an incidence of at least 2% in patients receiving treatment with various therapies for advanced melanoma (including T-VEC, ipilimumab, vemurafenib and dabrafenib) were included in the study, and the health state descriptions were validated by six healthcare professionals (three oncologists and three oncology nurses) experienced in the treatment of advanced melanoma.

Participants (n=300) were recruited from the general public in three different geographical locations across the UK and were asked to rate their own health using the EQ-5D-3L and Visual Analogue Scale (VAS), and also rate the health state descriptions using the VAS and TTO. The results from the study are detailed in Appendix 1.7 and show that the VAS scores and the mean TTO utility values for each health state trended in the direction expected for health state severity and as expected the mean utility values for PD, CR, and PR were the highest, and PD and BSC had the lowest utility values.

Stable disease was used as the anchoring state for the calculation of increments or decrements in utility, and further details on disutilities are provided in Section 5.4. The results from the TTO study have been explored in the sensitivity analysis, and further details on the identification of utility values for the cost-effectiveness model are described in Section 5.4, with the values implemented in the model presented in Section 5.6.

Consistency with NICE reference case

The FACT-BRM is not a preference based measure of HRQoL and does not conform to the NICE reference case.

Given that the trial based HRQoL data is inconsistent with the NICE reference case, HRQoL data from the literature has been used in the economic model which is consistent with previous NICE appraisals in metastatic melanoma[2,57,58].

Mapping

Mapping was not undertaken and the utility values utilised in the base-case modelling were based on a recent NICE TA in melanoma (TA321)[1]. The model also included disutilities from adverse events based on a preference elicitation study by Amgen (Section 5.4).

Health-related quality-of-life studies

Systematic searches for relevant HRQoL

A SLR was conducted in September 2015 to identify published HRQoL studies for advanced (unresectable or metastatic) melanoma.

Search strategy

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

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.
- PsycInfo (OvidSP): 1806 to September Week 1 2015

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

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

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

- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(http://www.ispor.org/)

- European Association of Dermato Oncology (EADO) (http://www.eado.org/)
- European Cancer Congress (ECC) (http://www.esmo.org/Conferences/European-Cancer-Congress-2015)
- Society of Melanoma Research (SMR) (http://www.societymelanomaresearch.org/)
- Perspectives in Melanoma (PIM) (http://imedex.com/perspectives-melanoma-conference/)

Additionally, a reference list review of reports identified through a manual search of HTA websites was also under taken for the:

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

Study selection

Study inclusion was not limited by language, HTA reviews were restricted to the UK (England, Scotland, Wales) and Canada, and the publication date for conference proceedings was limited to 2013. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 5-9.

Table 5-9: Study inclusion and exclusion criteria

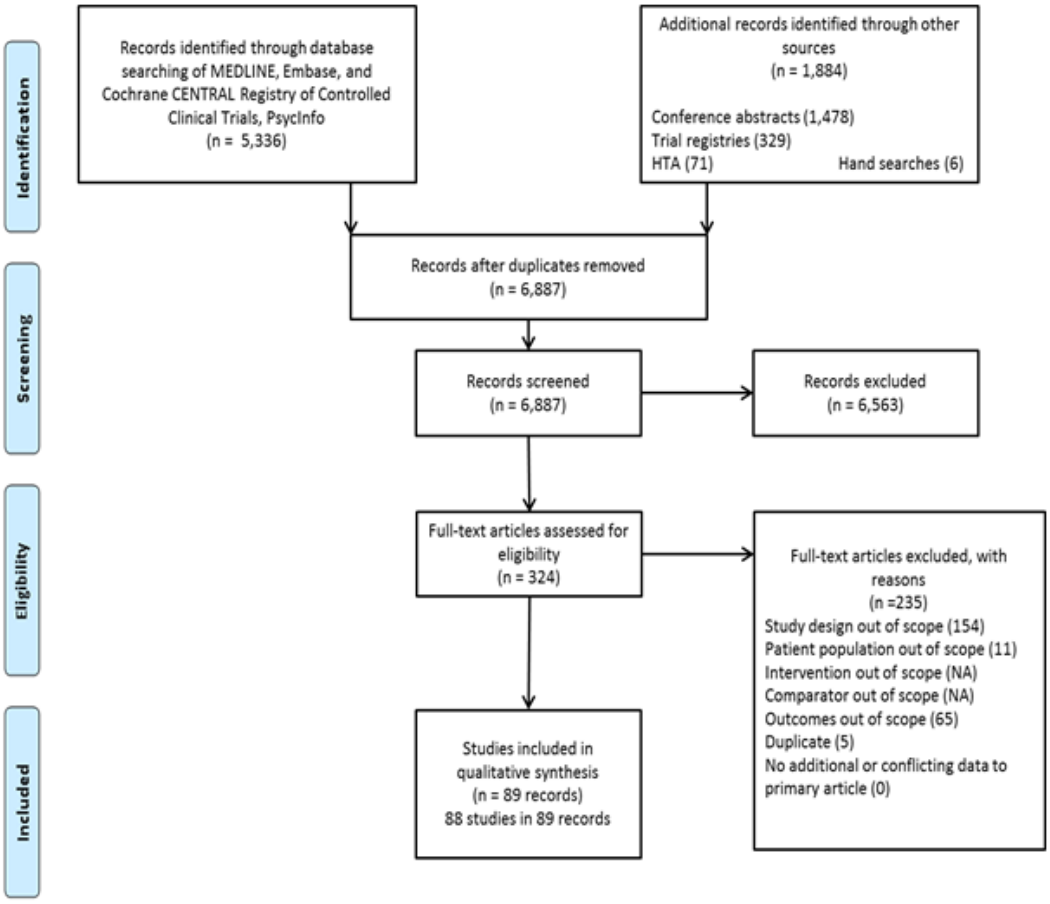
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of a mixed cancer populations not reporting results for melanoma separately
Intervention/Comparators	No restriction by treatment or comparator	Not applicable
Outcomes	• HRQoL data assessed by both generic and disease-specific instruments including the EQ-5D, FACT-BRM, EORTC QLQ-C30, and SF-12 SF-3) • Utility scores • Health state information • Patients satisfaction with treatment	Not applicable

	Inclusion criteria	Exclusion criteria
Study Design	• RCTs, including crossover studies; non-randomised clinical trials; • observational studies (prospective and retrospective cohort studies); • Surveys	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	Not applicable
Date restrictions	Conference proceedings 2013 – Present	Not applicable
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-BRM, Functional Assessment of Cancer Treatment-Biological Response Modifier; RCT, randomised controlled trial; SF, Short Form		

Study selection results for HRQoL evidence

The PRISMA flow diagram for the SLR is presented in Figure 5-28. A total of 7,220 records were retrieved from electronic databases (n=5,336), HTA assessments (n=71), clinical trial registry records (n=329), conference abstracts (n=1,478) and additional records identified from hand searching reference lists of existing systematic reviews (n=6). Following the removal of duplicate records, 6,887 titles and abstracts were screened and from these records, a total of 6,563 studies were excluded. Following the exclusion, 324 full-text records were screened to determine whether they fulfilled the review inclusion criteria and after detailed review, 89 records reporting data for 88 studies were selected as meeting all of the inclusion criteria and were extracted in full.

Figure 5-28: PRISMA flow diagram for HRQoL and Utility evidence



Details of the studies in which HRQoL was measured

Of the 88 studies that were extracted in full, 36 were conducted in patients with stage III – IV melanoma, 45 studies in patients with any stage melanoma, and 7 studies were in mixed cancer populations with results specifically reported for patients with melanoma.

Outcomes assessed included HRQoL, stress and anxiety, depression, fatigue, coping satisfaction with treatment, disease impact, social support/relationships, self-image and health-state utilities.

The most frequently used instruments to assess outcomes were the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-C30 (n=18), the Short Form (SF)-36 (n=9) and the Hospital Anxiety and Depression Scale (HAD) (n=9). Functional Assessment of Cancer Therapy-Melanoma (FACT-M) (n=6), EuroQOL (EQ-5D) (n=5), the State-Trait Anxiety Index (STAI) (n=5) and Beck Depression Inventory (BDI) (n=5), were used less frequently.

Of the 88 studies were identified in the SLR only 8 were deemed relevant to the decision problem (Table 5-10) in that they included a preference based quality of life instrument (e.g. EQ-5D, SF-36, SF-12, SF-6D or HUI)

Table 5-10: Details of the studies in which HRQoL was measured

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Stage III and IV melanoma					
Hatswell 2014[132]	Patients enrolled at 125 centres in 13 countries in North America, South America, Europe, and Africa UK / Utility	IPI+ gp100 IPI only gp100 only	Advanced or metastatic MEL	EORTC-8D SF-6D	EORTC-8D Progression: Pre-progression: 0.803 Post-progression: 0.755 Time to death: 180 or more days to death: 0.831 120 - 179 days to death: 0.771 90 - 119 days to death: 0.763 60 - 89 days to death: 0.720 30 - 59 days to death: 0.679 Under 30 days to death: 0.653 SF-6D Progression: Pre-progression: 0.642 Post-progression: 0.612 Time to death: 180 or more days to death: 0.667 120 - 179 days to death: 0.616 90 - 119 days to death: 0.613 60 - 89 days to death: 0.585 30 - 59 days to death: 0.557 Under 30 days to death:0.544

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Beusterien 2009[130]	UK and Australia / Cross-sectional, standard gamble	NA	Advanced MEL patients	Treatment response: WHO definition for all cancers Toxicity: common grade I/II toxicities from published and unpublished literature, and product inserts for IPI, DTIC, TMZ, IL-2, fotemustine, and IFN-α	Australia and UK Partial response 0.88 Table disease 0.80 Progressive disease 0.52 UK Partial response 0.85 Table disease 0.77 Progressive disease & BSC 0.59
CheckMate 066 2015[133]	ND / Phase III RCT	NA	Patients with advanced MEL	EQ-5D VAS EORTC global health	Non-progressive disease 0.77 Progressive disease 0.68
CheckMate 069 2015[134]	ND / Phase II trial	NA	Patients with metastatic or unresectable MEL	EORTC QLQ-C30 EQ-5D	ND
NICE TA321 2014[1]	UK / Technology submission and appraisal	Dabrafenib DTIC	Unresectable or metastatic MEL	EQ-5D	CR 0.77 PR 0.77 SD 0.77 PD 0.68
NICE TA268 2011[57]	UK / Technology submission and appraisal	IPI BSC, CT or DTIC	Advanced MEL patients	EQ-5D	Progression-free disease 0.81 Progressive disease 0.77
Any stage melanoma					
Mols 2010[135]	NL / Observational	NA	MEL survivors	SF-36 IOC	ND
Tromme 2014	Belgium / Utility	NA	MEL patients	EQ-5D-5L VAS FACT-M	Stage III-T From start of treatment 0.535 Stage IV-R From start of remission 0.796

Authors/Date	Setting	Interventions	Population	Methods of valuation	Utilities SD/SE/range or CI's
Abbreviations: Scale; CT = chemotherapy; DTIC = dacarbazine; EORTC = European Organisation for Research and Treatment of Cancer; EQ = EuroQOL;; GAD = General; HRQoL health-related quality of life; IFN = interferon; IL=2 = interleukin-2; IPI = ipilimumab; IPQ = Illness Perception Questionnaire; ISSS = Illness-Specific MEL = melanoma; ; ND = not documented; NL = Netherlands;; SF = Short Form; -Short Form;; TMZ = temozolomide; UK = United Kingdom; US = United States; VAS = Visual Analogue Score; VFB					

Key differences between values derived from the literature search and those reported in or mapped from the clinical trials

The trial based HRQoL data is inconsistent with the NICE reference case and has not been used in the economic analysis. Consequently, HRQoL data from the literature has been used in the economic model (Table 5-10).

Adverse events

AEs associated with therapy can have an impact on the quality of life of patients receiving treatment for metastatic melanoma.

T-VEC has a largely manageable safety profile with the most frequent events being pyrexia, chills, flu-like symptoms, and injection site reactions, most of which were non-serious and mild to moderate in severity (Section 4.13). Given the low incidence of grade ≥3 AEs in the OPTiM trial (2.1%), the model considers grade ≥3 AEs with an incidence of ≥2% as a conservative measure. This is in contrast with the ipilimumab NICE TA (TA319)[2] where the model considered grade ≥3 AEs with an incidence of ≥3%. This approach was deemed appropriate in this context given the very low incidence of adverse events observed in the OPTiM trial for T-VEC; the only AE of grade ≥3 occurring in 2.1% of patients was cellulitis. When considered in the context of the severity of uncontrollable metastatic melanoma, this was not considered to impact on patient's HRQoL. It is noteworthy that grade 1 or 2 AEs were not included in the model because it was assumed they would not be associated with any meaningful management costs or impact HRQoL. This approach was accepted by the appraisal committee in TA268[2].

The incidence rates of AE's included in the model are presented in Table 5-11. The incidence of all AEs was assumed to be annual and they were assumed to last one day; AE-related QALYs were calculated by multiplying the incidence of each AE (i.e., the probability of occurring) by its duration and the day equivalent of the disutility for that AE. These were then summed across all AEs and subtracted from the overall QALY gain for each treatment.

Table 5-11: Incidence of grade ≥3 AEs with an incidence of ≥2%

Grade ≥3 AEs	T-VEC[a] (%)	IPI[b] (%)
Anaemia	-	3.1
Cellulitis	2.1	-
Colitis	-	5.3
Constipation	-	2.3
Diarrhoea	-	5.3
Dyspnea	-	3.9
Fatigue	-	6.9
Headache	-	2.3
Nausea	-	2.3
Vomiting	-	2.3

AE, adverse events; IPI, ipilimumab; T-VEC, talimogene laherparepvec
[a] Source: Andtbacka et al. (2015)[79]. Includes AEs with an incidence ≥2%
[b] Source: Hodi et al. (2010)[72]. Includes AEs with an incidence of ≥3%

Health-related quality-of-life data used in cost-effectiveness analysis

Health states in terms of HRQoL in the cost-effectiveness analysis.

QALYs were calculated using area under the curve (AUC) methods. The Health State Utility Value (HSUV) for non-PD was assigned to patients in the non-PD health state. The HSUV for PD was assigned to patients in the PD health state (i.e., the difference between the OS and PFS curves in each cycle). The QALYs for non-PD and PD were summed by treatment arm over the 30-year horizon. The model also included disutilities for grade ≥3 AEs, obtained from a preference elicitation study (Appendix 1.7). Only one grade ≥3 AE, cellulitis (2.1%), was reported for patients on the T-VEC arm in the OPTiM trial[79]. The disutilities ≥3 AEs associated with the comparators are shown in Table 5-12.

Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness

Quality of life was assumed to remain constant in each health state.

Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

Description of how and why health state utility values used in the cost effectiveness analysis have been adjusted, including the methodologies used

Not applicable.

Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

As described in Section 5.4 only grade ≥3 AE's with an incidence of ≥2% were modelled for both T-VEC and ipilimumab.

Summary of utility values chosen for the cost-effectiveness analysis

Utility values used in the cost-effectiveness analysis are presented in Table 5-12.

Table 5-12: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Source
Base-case values				
CR	0.77 (0.011)	0.75-0.79	Section 5.4	TA321[1]
PR	0.77 (0.011)	0.75-0.79		
SD	0.77 (0.011)	0.75-0.79		
PD	0.68 (0.084)	0.52-0.85		
Alternative values used in scenario analyses				

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Source
CR	0.84 (0.011)	0.82-0.86	Section 5.4	Amgen, 2014 (utility study for advanced melanoma)[136]
PR	0.73 (0.011)	0.71-0.75		
SD	0.69 (0.011)	0.67-0.71		
PD	0.45 (0.084)	0.29-0.61		
CR	0.85 (0.011)	0.83-0.87	Section 5.4	Beusterin et al 2009[130]
PR	0.85 (0.011)	0.83-0.87		
SD	0.77 (0.011)	0.75-0.79		
PD	0.59 (0.084)	0.43-0.75		
CR	0.81 (0.011)	0.79-0.83	Section 5.4	TA268[57]
PR	0.81 (0.011)	0.79-0.83		
SD	0.81 (0.011)	0.79-0.83		
PD	0.77 (0.084)	0.61-0.93		
Disutilities associated with AEs				
Anaemia	0.09 (0.003)	0.083-0.097	Section 5.4	Amgen, 2014 (utility study for advanced melanoma) [136]
Cellulitis	0.12 (0.005)	0.111-0.129		
Colitis	0.26 (0.010)	0.241-0.280		
Constipation	0.14 (0.005)	0.130-0.151		
Diarrhea	0.11 (0.004)	0.102-0.118		
Dyspnea	0.11 (0.004)	0.102-0.118		
Fatigue	0.05 (0.002)	0.046-0.054		
Headache	0.16 (0.006)	0.148-0.172		
Nausea	0.26 (0.010)	0.241-0.280		
Vomiting	0.26 (0.010)	0.241-0.280		
AE, adverse event; CR, complete response; PD, progressive disease; PR, partial response, SD, stable disease				

Details if clinical experts assessed the applicability of the health state utility values available or approximated any of values

Not applicable.

5.5 Cost and healthcare resource use identification, measurement, and valuation

Parameters used to estimate cost-effectiveness

A summary of the variables used in the cost-effectiveness analysis is presented in Section 5.6.

Resource identification, measurement, and valuation studies

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

Search strategy

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

- MEDLINE (OvidSP): 1946 to present
- EMBASE (OvidSP): 1988 to 2015 (Week 35)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): August 2015.
- EconLit (OvidSP):1886 to August 2015
- NHSEED (OvidSP):2nd Quarter 2015

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

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

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

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

- Perspectives in Melanoma (PIM) (http://imedex.com/perspectives-melanoma-conference/)

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

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

Study selection

Study inclusion was not limited by language. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 5-13.

Table 5-13: Study inclusion and exclusion criteria

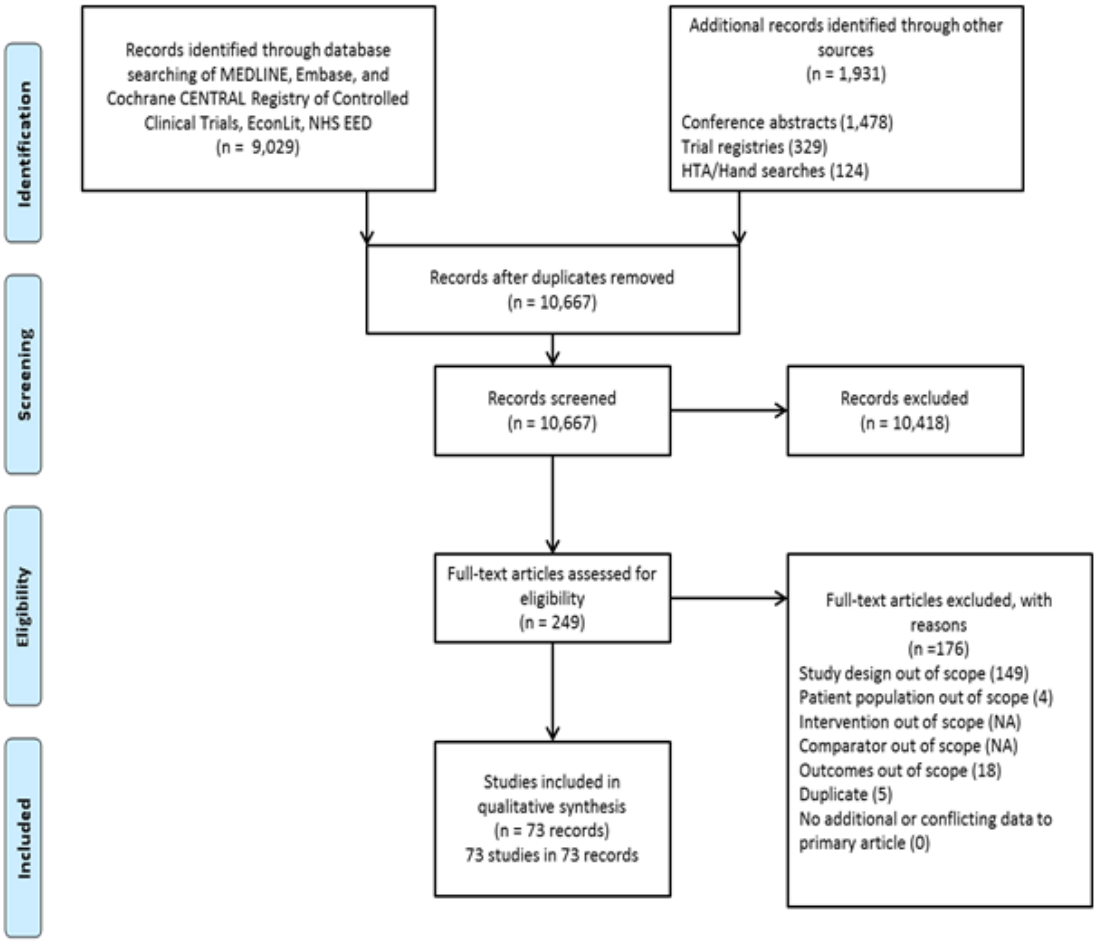
	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years of age) with any stage melanoma who are receiving treatment for the first time or have received prior treatment	• Studies including patients with non-cutaneous (e.g., ocular/uveal) melanoma and/or active cerebral or bone metastases. • Studies of a mixed cancer populations not reporting results for melanoma separately
Intervention/ Comparators	There was no restriction by treatment or comparator.	Not applicable
Therapeutic Area/ Conditions of Interest	Melanoma	Not applicable
Outcomes	Global healthcare resource use and global healthcare cost data	Not applicable
Study Design	Published cost or resource use documentation studies	Not applicable
Language restrictions	No restrictions	Not applicable
Country restrictions (HTAs only)	• UK • Canada	
Date restrictions	Not applicable	Not applicable

Study selection results for economic evaluation evidence

The PRISMA flow diagram for the SLR is presented in Figure 5-29. A total of 9,029 records were retrieved from electronic databases (n=9,029), HTA assessments (n=124), clinical trial registry records (n=329) and conference abstracts (n=1,478). Following the removal of duplicate records, 10,667 titles and abstracts were screened and from these records, a total of 10,418 studies were excluded. 249 full-text records that were remaining were screened to

determine whether they fulfilled the review inclusion criteria and after detailed review, 73 records reporting data for 73 studies were selected as meeting all of the inclusion criteria and were extracted in full.

Figure 5-29: PRISMA flow diagram for Resource Use



Description of Identified studies

To ensure the SLR captured sufficient relevant information to populate the economic model, the population criteria considered were broader than advanced melanoma and there was no restriction on the intervention. The majority of studies were conducted in the United States (n=24) and the United Kingdom (n=11), with other studies conducted in Europe (n=26), North America (n=4), Australia (n=3) and New Zealand (n=1).

The types of healthcare resource use examined included pharmacy resources (including drug costs, drug management and management of toxicity); surgical resources (including excisions and biopsies); laboratory resources (such as complete blood count and complete metabolic panels); imaging resources (such as computed tomography and positron emission tomography scans and x-rays; in-patient resources (such as hospitalisations, emergency room visits); outpatient resources including office visits, hospice resources including palliative and end-of-life care, and all associated costs.

Of the 11 UK sources, eight were deemed relevant to the decision problem and the decision making process in England and are summarised in Table 5-14.

The only study to formally report resource utilisation in terms of inpatient, outpatient and hospice care requirements is the MELODY study[137,138] and it represents the largest single study of resource utilisation in melanoma (n=220) reporting resource utilisation for a UK-specific cohort.

Table 5-14: Summary list of published cost-and resource use studies

First author, year	Study design	Intervention	Source for costing data	Cost type
NICE TA319 2014[2]	Technology submission and appraisal, including cost-utility analysis	IPI DTIC VEM	NHS and PSSRU references and Oxford outcomes Melanoma Resource Use report For the identification of IPI administration costs, existing CT delivery HRGs to cost its administration Existing literature	Treatment-specific costs Melanoma Resource Use
NICE TA269 2012[58]	Technology submission and appraisal, including cost-utility analysis	VEM DTIC	BRIM-3 trial, Robert trial, US SEER for patients with melanoma, the main sources of cost data are the NHS Reference Cost Schedule (09-10), the British National Formulary and the MS submitted for the NICE appraisal of IPI	Drug acquisition and administration Testing for BRAF V600 Cost of disease relate to health states and treating AEs
NICE TA321 2014[1]	Technology submission and appraisal, including cost-utility analysis	Dabrafenib DTIC VEM	Clinical data and HRQoL from BREAK3 trial; Data for VEM from BRIM-3 trial.	Drug costs, dispensing costs, administration costs, anti-cancer therapy after the study costs.
NICE TA268 2012[57]	Technology submission and appraisal, including cost-utility analysis	IPI BSC	MDX 010-20 trial, 10 economic evaluations; drug costs retrieved from British national formulary	Drug acquisition and administration costs Cost of the disease
Johnston 2012[137]	Retrospective analysis based on Melody (multinational, observational, longitudinal and retrospective study of	Systemic therapy BSC	UK cohort Hospitalisation: NHS Hospice: UK Consumer Price Indices Outpatient: NHS	Hospitalisation (per diem) Hospice (per diem) Outpatient (per visit)

First author, year	Study design	Intervention	Source for costing data	Cost type
	advanced melanoma patients)			
NICE TA357 2015[59]	Technology submission and appraisal, including cost-utility analysis	PEM BSC	KEYNOTE-002 Schadendorf et al. 2015 Balch et al. 2001 American Joint Committee on Cancer	Costs of treatment, monitoring and follow-up, management of complications and adverse events, and terminal care.
Lorigan 2014[138]	Multinational, observational, retrospective, longitudinal survey	ND	UK data collected from a multinational, observational, retro, longitudinal survey	Any hospitalisation Any hospice care Any outpatient care
Linker 2013[139]	Retrospective cost attribution analysis	IFN non-IFN	Medical records; British National Formulary; National Institute for Health Research costing template"	

AE, adverse event; BSC, best supportive care; DTIC, dacarbazine; HRG, healthcare resource group; IFN, interferon; IPI, ipilimumab; ND, not documented; NHS, national health service; PEM, pembrolizumab; PSSRU, Personal Social Services Research Unit; SEER, Surveillance Epidemiology and End Results registry; VEM, vemurafenib

NHS reference costs or payment-by results (PbR) tariffs

T-VEC is administered via intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. It is anticipated that administration of T-VEC will take place in a limited number of centres specialising in the treatment of skin cancers and it will be administered in an outpatient setting in a designated side room.

The HRG codes for chemotherapy delivery are described in Table 5-15. It is assumed that the cost of administering T-VEC would be equivalent to that of ipilimumab.

There are no HRG codes specific to T-VEC and there are no other chemotherapy treatments administered in a similar fashion to T-VEC, so it was therefore assumed that the cost of administering T-VEC would be equivalent to that of ipilimumab (HRG code SB13Z). This assumption is further supported by a study conducted by Amgen to understand the administration cost of T-VEC[140] (further details of the study are provided in Appendix 1.8).

Table 5-15: HRG codes for chemotherapy delivery

HRG code	Description
SB11Z	Deliver exclusively Oral Chemotherapy
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
SB15Z	Deliver subsequent elements of a chemotherapy cycle
SB16Z	Procure Chemotherapy drugs for regimens not on the national list
SB17Z	Deliver chemotherapy for regimens not on the national list
Source: NHS Reference Costs 2013-14[141]	

Clinical experts input

Resource costing study

The model incorporated data on healthcare resource utilisation for routine treatment, disease progression, and palliative care.

A treatment patterns survey and a costing study[140] were conducted to estimate healthcare resource utilisation associated with adopting T-VEC into routine clinical practice within the NHS. The study identified phases of resource use between active treatment and death in the advanced melanoma treatment pathway and was based on previous technology appraisals, an online survey of physicians, and international treatment guidelines.

Healthcare resource utilisation for BSC was derived from a NICE TA268 since the costing study did not distinguish BSC from palliative care[57].

For the costing study, a questionnaire was developed listing the resources such as consultations, monitoring, hospital visits, and surgical procedures that could be used in each

of these phases. Estimates of the magnitude (i.e., the percentage of patients utilising each resource item) and frequency of resource use per 3 or 6 months in clinical practice were obtained through consensus panels comprising experienced oncologists who treated patients with advanced melanoma. These were converted to estimated average monthly resource use per patient, as shown in Table 5-16.

In the non-PD health state, it was assumed that all patientswould receive routine care, irrespective of active treatment and response category (complete response, partial response, stable disease). This is a conservative assumption as it is plausible that patients who achieve a complete response may not require any routine care or require less than patients who achieve only partial response or have stable disease. As for patients with PD, all patients in non-PD health states were considered to receive BSC, irrespective of prior active treatment.

As described previously, monthly resource use for BSC was derived from NICE TA268[57] and calculated by multiplying the estimates of the magnitude by the frequency of BSC resource use. The data extracted from NICE TA268 are summarised in Table 5-16. The healthcare resource utilisation for terminal care was based on a microcosting study by the King's Fund[142]. In the model, patients who died were assumed to receive terminal care immediately prior to death.

Table 5-16: Monthly mean healthcare resource use per patient

Item	Routine treatment (units)	On progression (units)	Best supportive care[a] (units)	Palliative care (units)
Outpatient visits				
Medical oncologist	0.00	1.00	1.63	0.67
Radiation oncologist	0.03	0.10	0.06	0.00
General practitioner	0.33	0.00	0.08	0.53
Psychologist	0.03	0.00	0.00	0.05
Palliative care physician/nurse	0.00	0.00	0.00	0.13
Surgeon	0.02	0.05	0.03	0.02
Dermatologist	0.00	0.00	0.00	0.02
Oncology nurse	0.60	0.00	0.00	0.20
Inpatient stay				
Oncology ward	0.25	0.20	0.07	0.33
Day hospital	0.25	0.00	0.00	0.13
Emergency department	0.03	0.00	0.00	0.05
Home care				
Palliative care physician/nurse	0.00	0.00	0.00	0.50
Home aide visits	0.00	0.00	0.00	3.47

Item	Routine treatment (units)	On progression (units)	Best supportive care[a] (units)	Palliative care (units)
Laboratory tests				
Complete blood count	1.00	0.00	1.30	0.00
Complete metabolic panel	1.00	0.00	1.24	0.00
LDH measurement	0.00	0.00	1.24	0.00
Radiological exams				
Brain MRI	0.03	0.05	0.06	0.00
PET-CT scan	0.02	0.00	0.01	0.00
Bone scintigraphy	0.02	0.00	0.00	0.00
Chest radiograph	0.03	0.05	0.33	0.00
Brain CT	0.00	0.05	0.02	0.00
Whole-body CT	0.33	0.00	0.00	0.00
CT scan of abdomen/pelvis	0.00	0.00	0.38	0.00
CT scan of chest	0.00	0.00	0.38	0.00
Echography	0.00	0.00	0.04	0.00
Radiation oncology				
Stereotactic radiosurgery	0.00	0.20	0.00	0.00
Whole-brain radiation	0.00	1.00	0.00	0.00
Radiotherapy	0.07	0.20	0.00	0.00
Procedures				
Neurosurgery	0.00	0.10	0.00	0.00
Surgery (including biopsy and histopathology)	0.02	0.05	0.00	0.02

CT = computed tomography; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography.[a]

Source: NICE TA268, 2011[57]; Amgen, 2014[140]

Intervention and comparators' costs and resource use

The assumptions around dosing and consequent costs of treatment for T-VEC and the comparator treatments are described below.

Drug Acquisition Costs

The drug costs for T-VEC and ipilimumab are presented in Table 5-17 and the assumptions around dosing presented in Table 5-18. The drug acquisition cost for ipilimumab is based on its NHS list price and does not reflect the confidential PAS that is available for ipilimumab in the NHS. The drug acquisition cost for T-VEC is based on the anticipated list price of T-VEC. A PAS has been proposed for T-VEC and is currently under consideration by PASLU.

Table 5-17: Treatment cost per vial/pack

Treatment	Vial volume (mL)/ pack size	Cost per vial	Source
T-VEC	10^6pfu/mL x1mL vial 10^8pfu/mL x1mL vial	Anticipated list price £1,445 £1,445	BNF 2015[143]
Ipilimumab	10mL (50mg) vial 40mL (200mg) vial	NHS list price £3,750 £15,000	BNF 2015[143]

Table 5-18: Treatment Dosing Schedule*

Treatment	Dosage (including wastage)	Mean duration of treatment	Source
T-VEC	Cycle 1 (21 days): [redacted] vials of 10^6 pfu/mL Subsequent cycles (every 14 days): [redacted] vials of 10^8 pfu/mL	[redacted]	OPTiM[79]
Ipilimumab	52.20 mL every 3 weeks (1.22 x 10mL vials and 1.00 x 40mL vial)	10.50 weeks (3.5 administrations)	BMS (2015)[47]; Hodi et al. (2010)[72]
*All reported doses in the base case assume drug wastage			

T-VEC dose and treatment duration

The OPTiM study included 163 patients in the TVEC arm with stage IIIB-/IVM1a metastatic melanoma with non-visceral metastases[79]. Patients in the OPTiM trial remained on treatment for at least 6 months even in the event of disease progression (unless intolerability or alternate therapy was required based on assessment of the patient's clinical status)[79]. This is reflected in the anticipated marketing authorisation and is also reflected in the estimated of T-VEC dose and treatment duration.

In the OPTiM trial, an accelerated dosing schedule could be invoked, in which the frequency of injections into any progressing lesion(s) could be increased to once per week for 4 weeks and up to three sets of four accelerated injections could be given (as long as after each set of four accelerated injections, clinically relevant disease progression did not occur and there was still residual tumour to inject[79]. Accelerated dosing is not recommended in the anticipated license for T-VEC (refer to SPC; (Appendix 1.1). It is noteworthy that accelerated doses made up a very small proportion of doses administered (4.5%) in the trial and patients who received accelerated doses in the trial had poorer survival outcomes compared to patients who did not receive accelerated dosing. In routine clinical practice, it is anticipated that clinicians would not increase dosing frequency of T-VEC especially given that alternatives treatment options are available. Consequently the base-case analysis excludes accelerated doses.

In the OPTiM trial patients who had successfully completed treatment were eligible to enter into an extension study if they did not have disease progression during the OPTiM study or had a CR but developed new lesions within 12 months[81]. In the extension study patients continued with their randomised treatment allocation for an additional 6 months until CR, disease progression or unacceptable toxicity. A small proportion of patients (9.8%) on the T-VEC arm entered the extension phase. As a conservative measure, the base case analysis includes the doses that patients took in the extension study. It is noteworthy that all patients completed the extension phase in the final analysis. This provides complete information on T-VEC dosing and reduces the uncertainty regarding treatment duration (Section 5.5).

Individual patient-level data (IPD), relating to the use of T-VEC from the OPTiM study and the extension phase, was used to calculate the mean number of whole vials per injection day including wastage. This approach accounts for the observed numbers of whole vials used in order to accurately estimate the drug acquisition cost.

Mean injection days (i.e., visits where a patient received treatment) and mean number of whole vials per injection for T-VEC are reported in Table 5-19. The total mean number of vials is calculated using the total number of whole vials received by each patient over the time period.

The base case which excludes accelerated dosing but conservatively includes extension phase dosing, estimates a total number of [redacted] whole vials of T-VEC used in the model (Table 5-19).

Table 5-19: T-VEC dose assuming wastage used in the cost-effectiveness analysis (based on proposed licensed indication Stage IIIB-IVM1a)

T-VEC Dose Scenarios	First Dose (mL)	Subsequent Doses (mL)	Mean number of injections (including first injection)	Total number of vials (mL)
Exclude accelerated doses, exclude extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]
Exclude accelerated doses, include extension phase doses (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Include accelerated doses, include extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]
Include accelerated doses, exclude extension phase doses	[redacted]	[redacted]	[redacted]	[redacted]

Ipilimumab

The acquisition cost of ipilimumab is £3,750.00 per 10-mL vial and £15,000.00 per 40-mL vial[143]. For the base case, a mean number of 5.22 whole vials (including wastage) of ipilimumab per administration with 3.5 administrations was used as per TA319[2]. Although this estimate is not in line with the SPC and is indeed lower than the SPC recommended regimen, this conservative estimate (in favour of ipilimumab) has been used in the base case in the economic model.

Drug administration costs

The NHS reference costs for administration of ipilimumab and T-VEC are presented in Table 5-20. Both T-VEC and ipilimumab are considered to be administered as a day case, and the costs of administration are assumed to be similar at £317 (HRG code SB13Z).

Table 5-20: NHS reference costs and PSSRU costs – administration of treatments

Description	Source	Unit Price
Deliver more complex parenteral chemotherapy at first attendance- daycase	NHS Reference Costs[141] 2013/14 SB13Z	£316.95
NHS, National Health Service; PSSRU, Personal Social Services Research Unit		

Health-state unit costs and resource use

The systematic review of economic literature (Section 5.5), identified the MELODY study[137,138], a large study of resource utilisation in melanoma, reporting resource utilisation for a UK-specific cohort. These data were previously reported in NICE TA319[2] and subsequently in NICE TA357[59]. The following limitations relating to the MELODY study were noted in these appraisals:

- The study predated the new melanoma treatments currently approved and recommended.
- Patients were recruited 8-10 years ago, and as such the clinical landscape may differ considerably to UK practice today, particularly given the availability of ipilimumab and available treatments for BRAF-mutation positive melanoma.
- Dacarbazine, the most widely used treatment among patients in the MELODY study[138], is now used only when no active treatment is available.

Given the limitations of the MELODY study, Amgen commissioned a costing study to collect data on the costs associated with HRU use throughout the treatment pathway for advanced melanoma[140] described in Section 5.5. Using published literature and clinician input, four treatment phases were identified: active systemic treatment (pre-progression); disease progression; best supportive care (BSC)/palliative care; and terminal care. HRU elements were identified for each phase and estimates of the magnitude and frequency of use in clinical practice were obtained through a UK Delphi panel, comprising seven experienced oncologists.

The costs were then applied in the model as follows:

- Routine care costs: the unit costs of HRU for routine care of patients were multiplied by the monthly estimates of HRU to derive a monthly cost of routine treatment, which then

was converted to weekly costs and subsequently applied by cycle for patients with non-PD.

- On-progression costs: the unit costs of HRU for patients switching to PD were multiplied by the estimates of HRU. This was applied as a one-time cost for patients whose disease progressed.
- BSC costs: the unit costs of HRU for patients in BSC were multiplied by the monthly estimates of HRU for BSC. The monthly costs were converted to weekly costs and then applied by cycle for patients with PD until the administration of palliative care.
- Palliative care costs: the unit costs of HRU for patients in palliative care were multiplied by the monthly estimates of HRU for palliative care. The monthly costs were converted to weekly costs and then applied by cycle for patients with PD for 3 months prior to death. These costs were calculated separately from terminal care costs, to avoid overlapping of costs.
- Terminal care cost: the one-time cost of terminal care was applied to all patients who died.

The costs of disease management in the non-PD and the PD health states were irrespective of active treatment. Table 5-21 presents a summary of the resource use costs that are applied in the model

Table 5-21: Summary of resource use costs

Health state	Cost	Frequency
Non-progressive disease		
Routine treatment	£86.52	Per cycle
Progressive disease		
On progression	£1,198.50	One-off
Best supportive care	£91.24	Per cycle
Palliative care	£192.03	Per cycle
Terminal care	£6,105.00	One-off

The impact of the cost estimates for the non-progressive disease health state and the terminal care cost are explored in scenario analyses (Section 5.8). The impact of the BSC cost estimate is explored in the deterministic sensitivity analysis (Section 5.8).

Table 5-22 presents the detailed monthly HRU estimates and the corresponding unit costs according to health states. All data were obtained from NHS reference costs[141], the Personal Social Services Research Unit (PSSRU)[144], and NICE's TA 268[57]. A one-off cost of £6,105 for terminal care was obtained from the King's Fund[142]. All unit costs were inflated to 2013-2014 values, using the published inflation index from the PSSRU[144].

Table 5-22: List of health states and associated costs in the economic model

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
Non-progressive disease						

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
Routine treatment pre-progression: outpatient visits						Section 5.5
	Radiation oncologist	0.03	126.00	NHS Reference Costs (2013-2014)	800	
	General practitioner	0.33	46.00	PSSRU (2014)	NA	
	Psychologist	0.03	138.00	PSSRU (2014)	NA	
	Surgeon (cosmetic/ plastic)	0.02	93.00	NHS Reference Costs (2013-2014)	160	
	Oncology nurse	0.60	80.00	PSSRU (2014)	NA	
Routine treatment pre-progression: inpatient stay						Section 5.5
	Oncology ward	0.25	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Day hospital	0.25	513.00	NHS Reference Costs (2013-2014) (day case)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Emergency department	0.03	147.00	NHS Reference Costs (2013-2014), category 2 treatment (accident and emergency services)	VB07Z	
Routine treatment pre-progression: laboratory tests						Section 5.5
	Complete blood count	1.00	3.00	NHS Reference Costs (2013-2014)	DAPS05	
	Complete metabolic panel	1.00	1.00	NHS Reference Costs (2013-2014)	DAPS04	
Routine treatment pre-progression: radiological exams						Section 5.5
	Brain MRI	0.03	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
	PET-CT scan	0.02	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	Bone scintigraphy	0.02	183.00	NHS Reference Costs (2013-2014)	RA35Z	
	Chest radiograph	0.03	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Whole-body CT	0.33	146.00	NHS Reference Costs (2013-2014)	RA14Z	
Routine treatment pre-progression: radiation oncology						Section 5.5
	Radiotherapy	0.07	533.00	NHS Reference Costs (2013-2014)	SC45Z/SC46Z	
Routine treatment pre-progression: procedures						Section 5.2
	Surgery (including biopsy and histopathology)	0.02	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	
Progressive disease						
On progression: outpatient visits						Section 5.5
	Medical oncologist	1.00	140.00	NHS Reference Costs (2013-2014)	370	
	Radiation oncologist	0.10	126.00	NHS Reference Costs (2013-2014)	800	
	Surgeon (cosmetic/ plastic)	0.05	93.00	NHS Reference Costs (2013-2014)	160	
On progression: inpatient stay						Section 5.5
	Oncology ward	0.20	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
On progression: radiological exams						Section 5.5
	Brain MRI	0.05	170.00	NHS Reference Costs (2013-	RA01A/RA02A/RA03	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				2014)	Z	
	Chest radiograph	0.05	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Brain CT	0.05	104.00	NHS Reference Costs (2013-2014)	RA08A/RA09A/RA10Z	
On progression: radiation oncology						Section 5.5
	Stereotactic radiosurgery	0.20	978.00	NHS Reference Costs (2013-2014)	SC52Z	
	Whole-brain radiation	1.00	644.00	NHS Reference Costs (2013-2014)	SC46Z	
	Radiotherapy	0.20	533.00	NHS Reference Costs (2013-2014)	SC45Z/SC46Z	
On progression: procedures						Section 5.5
	Neuro-surgery	0.10	£181.00	NHS Reference Costs (2013-2014)	150	
	Surgery (including biopsy and histopathology)	0.05	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	
Best supportive care: outpatient visits						Section 5.5
	Medical oncologist	1.63	140.00	NHS Reference Costs (2013-2014)	370	
	Radiation oncologist	0.06	126.00	NHS Reference Costs (2013-2014)	800	
	General practitioner	0.08	46.00	PSSRU (2014)	NA	
	Surgeon (cosmetic/ plastic)	*0.03*	*93.00*	*NHS Reference Costs (2013-2014)*	*160*	
Best supportive care: inpatient stay						Section 5.5
	Oncology ward	0.07	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				stay) excess bed days)	JD07H/JD07J/JD07K	
Best supportive care: laboratory tests						Section 5.5
	Complete blood count	1.30	3.00	NHS Reference Costs (2013-2014)	DAPS05	
	Complete metabolic panel	1.24	1.00	NHS Reference Costs (2013-2014)	DAPS04	
	LDH measurement	1.24	1.00	NHS Reference Costs (2013-2014)	DAPS04	
Best supportive care: radiological exams						Section 5.5
	Brain MRI	0.06	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	PET-CT scan	0.01	170.00	NHS Reference Costs (2013-2014)	RA01A/RA02A/RA03Z	
	Chest radiograph	0.33	98.00	NHS Reference Costs (2013-2014)	RA16Z	
	Brain CT	0.02	104.00	NHS Reference Costs (2013-2014)	RA08A/RA09A/RA10Z	
	CT scan of abdomen/pelvis	0.38	104.00	NICE TA319	RA08A/RA09A/RA10Z	
	CT scan of chest	0.38	104.00	NICE TA319	RA08A/RA09A/RA10Z	
	Echography	0.04	65.00	NHS Reference Costs (2013-2014)	RA60A	
Palliative care: outpatient visits						Section 5.5
	Medical oncologist	0.67	140.00	NHS Reference Costs (2013-2014)	370	
	General practitioner	0.53	46.00	PSSRU (2014)	NA	
	Psychologist	0.05	138.00	PSSRU (2014)	NA	
	Palliative care physician/nurse	0.13	143.00	NHS Reference Costs (2013-2014)	SD04A	

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
	Surgeon (cosmetic/ plastic)	0.02	93.00	NHS Reference Costs (2013-2014)	160	
	Dermatologist	0.02	98.00	NHS Reference Costs (2013-2014)	330	
	Oncology nurse	0.20	80.00	PSSRU (2014)	NA	
Palliative care: inpatient stay						Section 5.5
	Oncology ward	0.33	258.00	NHS Reference Costs (2013-2014) (non-elective inpatients—(long stay) excess bed days)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Day hospital	0.13	513.00	NHS Reference Costs (2013-2014) (day case)	JD07A/JD07B/JD07C/JD07D/JD07E/JD07F/JD07G/JD07H/JD07J/JD07K	
	Emergency department	0.05	147.00	NHS Reference Costs (2013-2014), category 2 treatment (accident and emergency services)	VB07Z	
Palliative care: home care						Section 5.5
	Palliative care physician/nurse	0.50	153.00	PSSRU (2014)	NA	
	Home aide visits	3.47	124.00	PSSRU (2014)	NA	
Palliative care: procedures						Section 5.5
	Surgery (including biopsy and histopathology)	0.02	135.00	NHS Reference Costs (2013-2014)	100 and DAPS02	Section 5.5
Death						
Terminal care	Total one-off cost	NA	6105.00	Improving choice at end of life,	NA	Section 5.5

Health state	Items	Monthly resource use	Unit cost (£)	Source	Code(s)	Reference in submission
				Kings Fund (2008); inflated to 2014		

Abbreviations: CT, computed tomography, LDH, lactate dehydrogenase, MRI, magnetic resonance imaging; NA, not applicable; NHS, National Health Service; PET, positron emission tomography, PSSRU, Personal Social Services Research Unit.

Source: Addicott and Dewar 2008[142]; Department of Health 2014[141]; NICE 2014 (TA319)[2]; PSSRU 2014[144]

Adverse events unit costs and resource use

Costs for managing AEs were included for all grade 3 or 4 AEs with an incidence of at least 2% in patients receiving any of the treatment options. These AEs were assumed to occur once in the model and persist for 1 day (Section 5.3.3). The costs were mainly derived from NICE TA319[2] and NICE TA269[58], were inflated to the present year and are consistent with those reported in TA357[59]. All costs for managing AEs that are included in the model are presented in Table 5-23.

The costs for managing nausea and vomiting were assumed to be the same as for managing diarrhea, and the cost for managing anaemia was assumed to be the same for managing fatigue. These assumptions are consistent with NICE TA357[59]. Costs for managing cellulitis, constipation, or headache were not available from previous submissions, so the cost of managing cellulitis was assumed to be the same for managing rash in NICE TA269[58]. and the cost for managing headache was assumed to be the same as for managing pain in NICE TA357[59]. The cost of managing constipation and dyspnea was assumed to be £0 based on NICE TA319[2].

It should be noted that all endocrine disorders were included in NICE TA269[58] because they are known to be a serious event associated with treatment with ipilimumab. However, endocrine disorders were not included in our model because the incidence was less than 2% (0.4%). The omission of endocrine disorders was considered to be a conservative assumption when comparing AE costs with T-VEC.

Table 5-23: List of adverse reactions and summary of costs in the economic model

AEs	Items	Value	Source
Anaemia	Inpatient cost	£596.38 (50%)	Cost assumed to be the same as for fatigue in NICE TA319
	Outpatient cost	£156.84 (50%)	
	Average cost per patient	£376.61	
Cellulitis	NR	£137.31	Cost assumed to be the same as for rash in NICE TA269 and inflated to 2014 cost
Colitis	Inpatient cost	£1,011.21 (100%)	NICE TA319 inflated to 2014 costs
Constipation	NA	£0	Cost assumed to be £0
Diarrhoea	Inpatient cost	£838.46 (50%)	NICE TA319 inflated to 2014 costs
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£491.26	
Dyspnoea	NA	£0	NICE TA319; cost assumed to be £0
Fatigue	Inpatient cost	£596.38 (10%)	NICE TA319 inflated to 2014 costs
	Outpatient cost	£156.84 (90%)	
	Average cost per patient	£200.79	
Headache	Outpatient cost	£171.86 (100%)	Cost assumed to be the same as for pain in NICE TA357
Nausea	Inpatient cost	£838.46 (50%)	Cost assumed to be the same as for diarrhoea in NICE TA319
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£213.49	
Vomiting	Inpatient cost	£838.46 (50%)	Cost assumed to be the same as for diarrhoea in NICE TA319
	Outpatient cost	£144.05 (50%)	
	Average cost per patient	£213.49	
AE, adverse event; NA, not applicable; NHS, National Health Service; NR, not reported; PPE, palmar-plantar erythrodysesthesia Source: NICE TA269[58]; NICE TA319[2]; NICE TA357[59]			

Miscellaneous unit costs and resource use

Not applicable.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

A list of parameters used in the cost-effectiveness model is detailed in Appendix 1.6.

Base case de novo analysis

The base-case cost-effectiveness analysis reflects the NICE reference case.

Assumptions

All assumptions that were used to support the construction of the economic model are described in Table 5-24.

Table 5-24: List of assumptions used in the economic model

Area	Assumption	Justification
Population	The endpoints studied in the OPTiM trial are applicable to all patients independent of their BRAF status.	The results from the OPTiM trial did not suggest that the efficacy of T-VEC is dependent on BRAFv600 mutation status.
Comparator	Although the relevant comparators as defined in the final scope are ipilimumab, vemurafenib (BRAFv600 positive mutation) and dabrafenib (BRAFv600 positive mutation), the cost-effectiveness analysis presents results versus ipilimumab only.	These are treatments which are approved by NICE for use in the NHS in England and included in the final scope of this appraisal. The adjustment using the Korn model was deemed inappropriate, and consequently the results unreliable, for the BRAF-inhibitors. In addition, ipilimumab is deemed to be a key comparator given that it is an immunotherapy like T-VEC and is likely to be used in clinical practice to treat patients in the early stage disease whereas the BRAF inhibitors are likely to be reserved for severe patients who need a quick response.
Time horizon	30 years	This captures the lifetime time horizon (<5.72% of patients alive at this point) in line with the NICE reference case. The average age of patients in the model is 67 and a 30 year time horizon is long enough to reflect the difference in costs and outcomes between T-VEC and ipilimumab.
Treatment pathway	A three state model was used where patients are followed through three health states: • Non-progressive disease • Progressive disease • Death	Three state models have been used in previous melanoma appraisals and deemed acceptable by NICE.
Efficacy	It is plausible that T-VEC has a better chance of improving survival in its anticipated licensed population versus ipilimumab over time and at worst T-VEC is expected to be no less effective.	Given the issue of broken networks and the heterogeneity between OPTiM and the ipilimumab trials, the Korn model adjustments (modified Korn approach and the two-step Korn approach) were applied to estimate the survival for ipilimumab compared to T-VEC. Both

Area	Assumption	Justification
		cost and clinical outcomes are extrapolated beyond observed follow-up periods. For clinical outcomes, the methods used to perform this extrapolation are presented in Section 4.11. The use of AJCC registry and Office of National Statistics data after 4.58 years and 5.17 years for ipilimumab and T-VEC respectively assumes that there is no difference in the risk of death between T-VEC and ipilimumab after this point.
HRQoL	The quality of life of patients was captured by progression-based utilities through EQ-5D and was taken from the NICE melanoma appraisal TA321. The health state utility value for patients in the pre-progression disease state and post-progression disease state was summed by treatment arm over the model horizon.	Evaluation of HRQoL through EQ-5D using the validated, generic, choice-based EQ-5D is consistent with the NICE reference case.
Safety	The incidence of AEs from OPTiM trial was assumed to reflect that observed in clinical practice. The costs associated with AEs grade 3 and above with an incidence greater than 2% were included in the cost-effectiveness model.	Previous submissions in melanoma considered the inclusion of AEs grade 3 and above regardless of incidence. Given that the OPTiM trial reported only one AE for the T-VEC arm that was grade 3 and above and given that this AE is captured in the cost-effectiveness model, this assumption is conservative in favour of comparator ipilimumab.
Costs	Vial sharing is not allowed.	Vial sharing has not been accepted by NICE in previous submissions. The base case therefore assumes no vial sharing and the number of vials calculated and used in the model is based on whole vials and includes wastage.
	Palliative care assumes BSC for three months prior to death.	In TA319, palliative care assumed BSC for 3 months prior to death. This was assessed in sensitivity analysis.
Resource use	Resource use data was based on an Amgen costing study which estimated health resource use associated with the treatment of metastatic melanoma based on country-specific treatment pathways including the UK.	Resource use data based on the MELODY study has been used in previous melanoma appraisals. This was assessed in sensitivity analysis as an alternative source of data on resource use.

Source: Andtbacka 2015[79], NICE 2013[125], NICE TA 319[2], Johnston 2012[137]; Lorigan 2014[138]

AE, adverse event; AJCC, American Joint Committee on Cancer; BSC, best supportive care;

Area	Assumption	Justification
HRQoL, health-related quality of life; T-VEC, talimogene laherparepvec		

5.7 Base-case results

Base-case cost-effectiveness results

The results of the economic model for patients with non-visceral metastatic melanoma (stage IIIB/C and IVM1a), are presented below in Table 5-25.

Using the modified Korn adjustment, the estimated mean OS was 6.66 years for patients treated with T-VEC and 4.90 years for patients treated with ipilimumab. Patients treated with T-VEC accrued 4.91 QALYs compared with 3.57 QALYs among patients on ipilimumab.

Using the two-step Korn adjustment, the estimated mean overall survival was 6.66 years for patients treated with T-VEC and 6.16 years for patients treated with ipilimumab. Patients treated with T-VEC accrued 4.95 QALYs compared with 4.61 QALYs among patients treated with ipilimumab.

Base-case incremental cost effectiveness analysis results

There is robust RCT data for T-VEC in the non-visceral metastatic disease (stage IIIB-IVM1a) population that demonstrates a significant OS gain. However, there is a dearth of data for the comparators in this patient population and consequently the clinical issue of the presence and the magnitude of interaction with treatment effect for the comparators in the T-VEC patient population is unknown. There is therefore genuine uncertainty around the “true” estimate of ipilimumab efficacy in patients with non-visceral metastatic disease (stage IIIB-IVM1a). The modified Korn adjustment accounts only for prognostic variability and may not include any potential treatment interaction effect for ipilimumab. The two-step Korn adjustment, in contrast, bestows the full treatment interaction effect based on a small subgroup of patients. The efficacy of ipilimumab is likely to lie between these two approaches of adjustment using the Korn model. For this reason, both are presented as a base case to reflect both ends of the spectrum.

T-VEC is a cost-effective option when compared with ipilimumab at the usual ICER thresholds accepted by NICE. Table 5-25 below presents the base case incremental cost-effectiveness results for comparison of T-VEC and ipilimumab in patients with non-visceral metastatic disease. It should be noted that these results are based on the anticipated list price for T-VEC and the NHS list price ipilimumab. Ipilimumab is available with a confidential PAS by way of a simple discount to the NHS; however, there is a lack of publicly available information regarding the PAS for ipilimumab. A comparison of the ICERs in a range of simple discounts (from 0%-100%) to reflect the possible PAS for ipilimumab is presented in Table 5-26 below.

T-VEC resulted in 1.34 additional QALYs and an additional cost of [redacted] when using the modified Korn method. When using the two-step Korn method, T-VEC resulted in 0.35 additional QALYs with an additional cost of [redacted]. As shown by the base-case results, the modified Korn method and the two-step Korn method demonstrate that based on anticipated

list price, T-VEC is cost-effective when compared with ipilimumab based on NHS list price at the usual ICER thresholds accepted by NICE (Table 5-25).

In the analyses that used the modified Korn method and compared T-VEC with ipilimumab in a range of potential PAS discounts, the ICER remained below a threshold of £20,000 per QALY when a 35% discount was assumed [redacted]. The ICER remained below a threshold of £30,000 per QALY when a 55% discount was assumed [redacted]; Table 5-26).

In the analyses that used the two-step Korn method and compared T-VEC with ipilimumab in a range of potential PAS discounts, the ICER remained below a threshold of £20,000 per QALY when a 5% discount was assumed [redacted]. The ICER remained below a threshold of £30,000 per QALY when a 10% discount was assumed ([redacted]; Table 5-26).

Table 5-25: Base-case results (discounted, considering anticipated and current NHS list prices)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Modified Korn							
IPI	98,219	4.90	3.57	-	-	-	-
T-VEC	[redacted]	6.66	4.91	[redacted]	1.76	1.34	[redacted]
Two-Step Korn							
IPI	96,035	6.16	4.61	-	-	-	-
T-VEC	[redacted]	6.66	4.95	[redacted]	0.50	0.35	[redacted]
ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; LYG, life years gained; QALYs, quality-adjusted life years; T-VEC, talimogene laherparepvec							

Table 5-26: Comparison of ICERs assuming a range of potential discounts for ipilimumab with anticipated list price for T-VEC

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
0%	[redacted]	[redacted]
5%	[redacted]	[redacted]
10%	[redacted]	[redacted]
15%	[redacted]	[redacted]
20%	[redacted]	[redacted]
25%	[redacted]	[redacted]
30%	[redacted]	[redacted]
35%	[redacted]	[redacted]
40%	[redacted]	[redacted]
45%	[redacted]	[redacted]
50%	[redacted]	[redacted]
55%	[redacted]	[redacted]
60%	[redacted]	[redacted]

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
65%	[redacted]	[redacted]
70%	[redacted]	[redacted]
75%	[redacted]	[redacted]
80%	[redacted]	[redacted]
85%	[redacted]	[redacted]
90%	[redacted]	[redacted]
95%	[redacted]	[redacted]
100%	[redacted]	[redacted]

Clinical outcomes from the model

A comparison of the clinical outputs estimated by the model and those obtained from the OPTiM clinical trial and the ipilimumab clinical trials is presented in Table 5-27. The comparison shows that the results for T-VEC estimated by the economic model are similar to those reported in the OPTiM trial. The median OS for T-VEC was estimated to be 4.01 years. This was 0.10 years higher than the median OS observed in the OPTiM trial (3.91 years). The restricted mean OS at 5 years was estimated to be 3.07 years. This was 0.21 years lower than the restricted mean OS observed in the OPTiM trial (3.28 years). The median PFS was estimated to be 1.09 years and was in line with the median PFS observed in the OPTiM trial. The percentage of patients with PFS at 0.5 years was estimated to be 65.97%. This was 2.39% lower than the value observed in the OPTiM trial. The similarity of the results suggests that the short-term and long-term outcomes from the model are valid for T-VEC.

The Korn methodology (modified Korn adjustment and two-step Korn adjustment were applied to estimate the survival of ipilimumab in the anticipated T-VEC licensed population. Given that the adjustment shifted upwards the survival curves for ipilimumab in this patient population with non-visceral metastatic disease, the comparison of the outputs estimated by the model based on the Korn methods of adjustment and the outputs from the clinical trials for ipilimumab which studied mostly patients with later stage metastatic disease are different. Using the modified Korn method, the model estimated the median OS for ipilimumab to be 1.71 years. This was 0.79 years and 0.86 years higher than the median OS observed in the first-line and second-line ipilimumab trials, respectively. The restricted mean OS at 5 years was estimated to be 2.37 years. This was 0.7 years and 0.8 years higher than the ipilimumab trials. The median PFS for ipilimumab estimated by the model using the modified Korn method was 0.56 years. This was 0.33 years higher than the median OS observed in both the first-line and second-line ipilimumab trials. The percentage of patients with PFS at 0.5 years was estimated to be 52.75% using the modified Korn method. This was 20.9% and 31.0% higher than the values observed in the first-line and second-line ipilimumab trials, respectively.

Using the two-step Korn method, the model estimated the median OS for ipilimumab to be 3.87 years. This was 3.09 years and 3.16 years higher than the median OS observed in the first-line and second-line ipilimumab trials, respectively. The restricted mean OS at 5 years

was estimated to be 2.91 years. This was 1.24 years and 1.34 years higher than the ipilimumab trials. The median PFS for ipilimumab estimated by the model using the two-step Korn method was 1.11 years. This was 0.88 years higher than the median OS observed in both the first-line and second-line ipilimumab trials. The percentage of patients with PFS at 0.5 years was estimated to be 66.83% using the two-step Korn method. This was 34.98% and 45.08% higher than the values observed in the first-line and second-line ipilimumab trials, respectively.

Table 5-27: Summary of model results compared with clinical data

	Model Results				Clinical Trial Results			
	Modified Korn		Two-Step Korn		T-VEC (OPTiM)	Ipilimumab		Ipilimumab
						CA184-024	MDX010-20	CA184-024 and MDX010-20
Outcome	**T-VEC**	**Ipilimumab (pooled)***	**T-VEC**	**Ipilimumab (pooled)***	**Previously Treated and Untreated**	**Previously Untreated**	**Previously Treated**	**Pooled* (previously untreated and treated)**
Median OS (years)	4.01	1.71	4.01	3.87	3.91	0.92	0.84	0.90
Restricted mean OS (5 years)	3.07	2.37	3.07	2.91	3.28	1.67	1.57	1.62
Median PFS (years)	1.09	0.56	1.09	1.11	1.09	0.23	0.23	0.23
% patients with PFS at 0.5 years	65.97%	52.75%	65.97%	66.83%	68.36%	31.85%	21.75%	28.23%
OS, overall survival; PFS, progression free survival; T-VEC, talimogene laherparepvec ; 8pooled using modified Mantel-Haenszel method (Appendix 1.10)								

Proportion of the cohort in the health state over time (Markov trace) for each state

Figure 5-30 and Figure 5-31 illustrate how patients move through the model health states over time when treated with T-VEC and ipilimumab, respectively, using the modified Korn method. Similarly, Figure 5-32 and Figure 5-33 illustrate how patients move through the model health states over time when treated with T-VEC and ipilimumab, respectively, using the two-step Korn method.

Figure 5-30: Markov trace for T-VEC: modified Korn

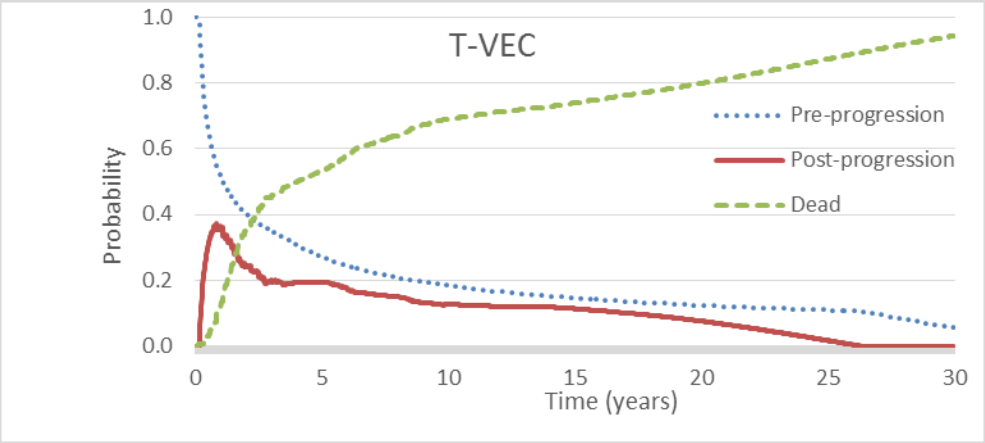


Figure 5-31: Markov trace for ipilimumab: modified Korn

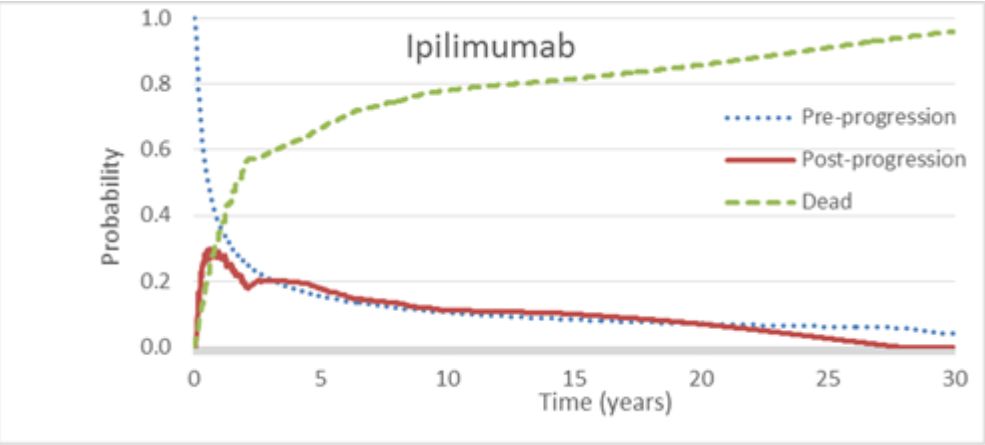


Figure 5-32: Markov trace for T-VEC: two-step Korn

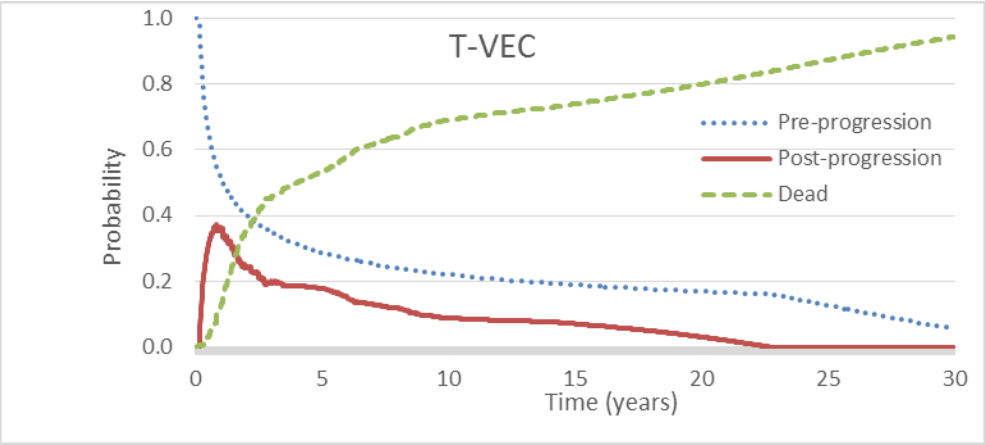


Figure 5-33: Markov trace for ipilimumab: two-step Korn

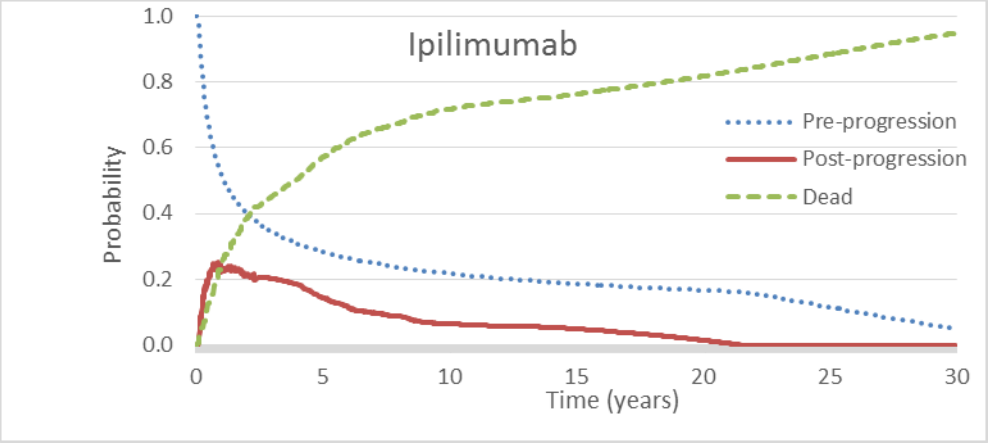
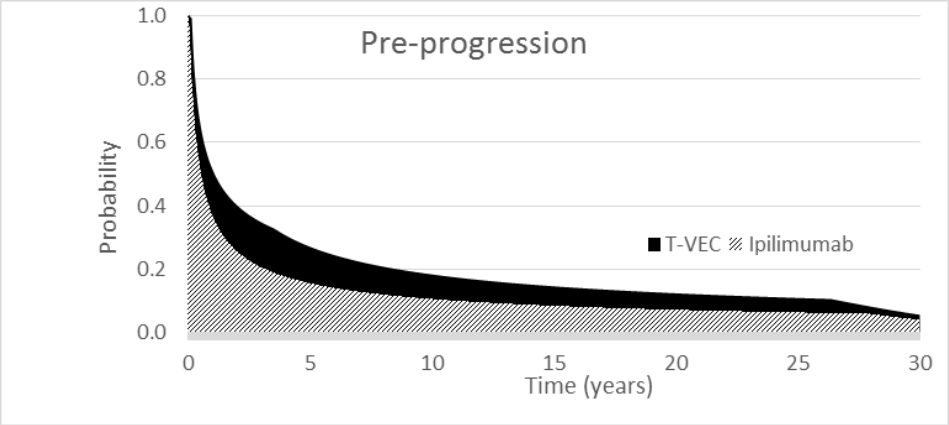


Figure 5-34 shows the proportion of patients who are in the pre-progression health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. When using the modified Korn method, the results show patients treated with T-VEC spend longer in the pre-progression health state than do patients treated with ipilimumab (Figure 5-34a). This is due to the improved PFS associated with T-VEC as seen in the OPTiM clinical trial Table 5-27. However, this effect is less pronounced when the two-step Korn method is used (Figure 5-34b); the median PFS for T-VEC and ipilimumab are almost identical. This is due to the significant adjustment ascribed to ipilimumab with the two-step Korn adjustment, which increases its PFS almost fivefold compared to that observed in clinical trials (Table 5-27).

Figure 5-34: Markov trace for the pre-progression health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment

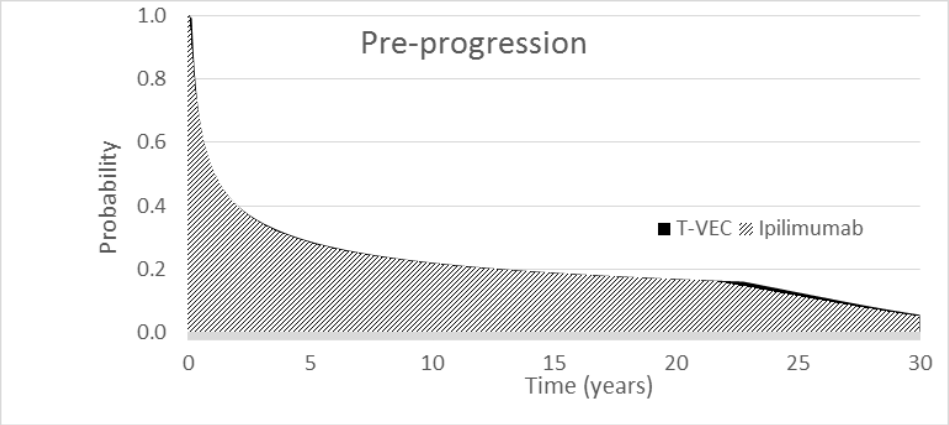


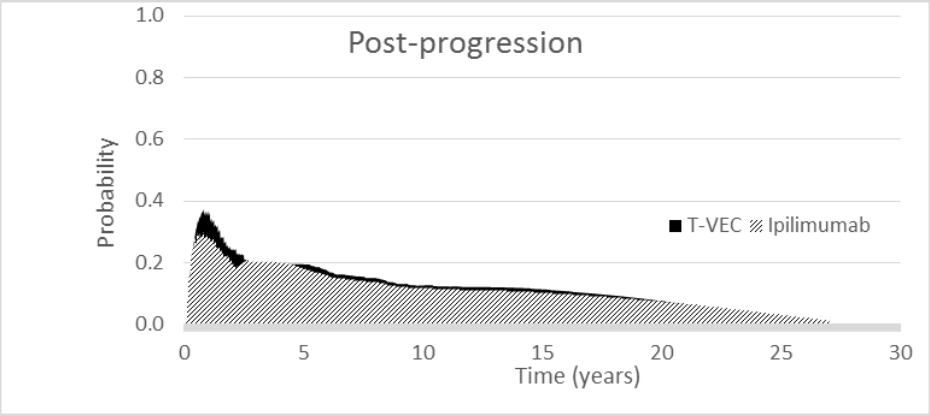
Figure 5-35 shows the proportion of patients who are in the post-progression health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. When using the modified Korn method, the results show that more patients treated with T-VEC remain in the post-progression health state than do patients treated with ipilimumab (Figure 5-35a and Figure 5-35b). This is driven by the improved OS associated with T-VEC (Table 5-27).

The same is true when using the two-step Korn method. Overall, more patients treated with T-VEC remain in the post-progression health state. However, the survival gain for T-VEC is less pronounced given that this method ascribed the full interaction effect for ipilimumab, significantly boosting the OS for ipilimumab in a population aligned with the anticipated T-VEC license (Table 5-27).

The proportion of patients in the post-progression health state is higher for ipilimumab between 2.7 years and 3.9 years using both the modified Korn and two-step Korn methods. This reflects the period where the modified Korn adjusted and the two-step Korn adjusted Kapan-Meier OS is higher for ipilimumab compared with T-VEC.

Figure 5-35: Markov trace for the post-progression health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment

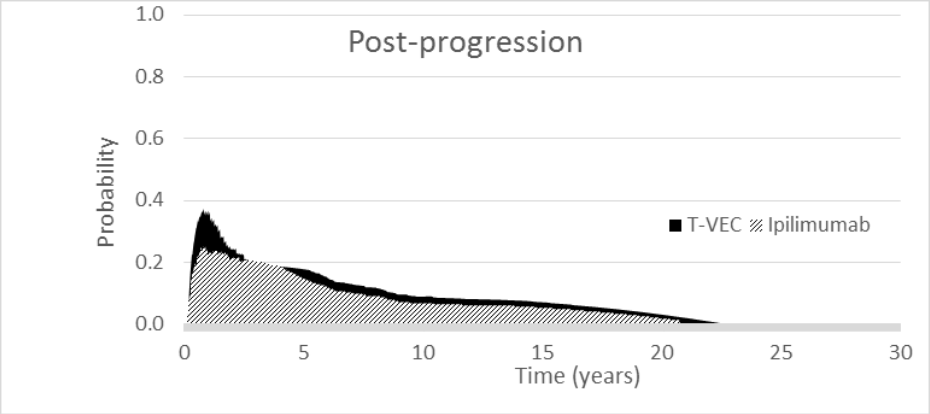
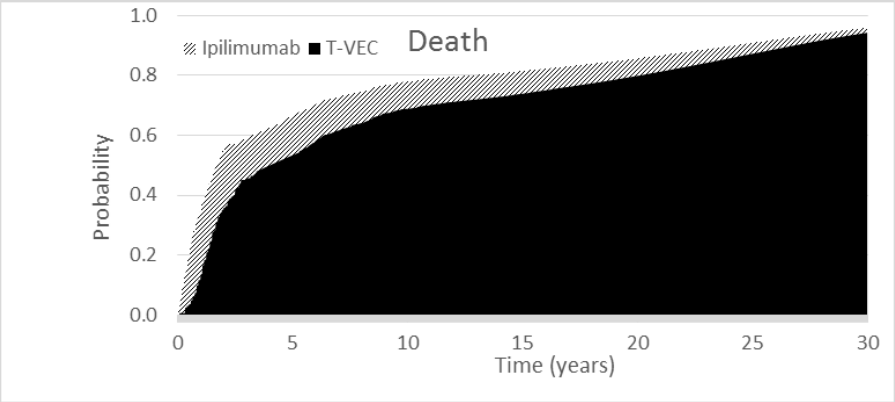


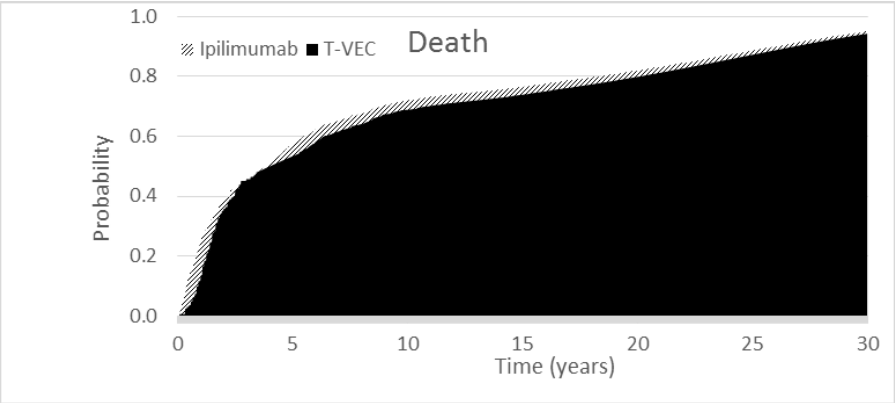
Figure 5-36 shows the proportion of patients who are in the death health state over time for T-VEC and ipilimumab, using the modified Korn and two-step Korn methods. The figure demonstrates the improved OS for patients treated with T-VEC.

Figure 5-36: Markov trace for the death health state for T-VEC versus ipilimumab: modified Korn (a) and two-step Korn (b)

a. Using modified Korn adjustment



b. Using two-step Korn adjustment



Details of how the model assumes QALYs accrued over time

Figure 5-37, Figure 5-38, and Figure 5-39 shows how the costs, QALYs, and life-years accumulate over time, respectively, for patients treated with T-VEC and ipilimumab using the modified Korn and two-step Korn methods. In the base case, QALYs are accrued according to progression status over time as previously reported.

Total costs initially are similar for T-VEC and ipilimumab, but T-VEC becomes more expensive after approximately 1.72 years using the modified Korn approach and after approximately 0.96 years when using the two-step Korn approach (Figure 5-37). This increase is driven by the increased cost of BSC and/or palliative care accrued by patients who receive T-VEC live longer and therefore remain in the progressive disease health state for longer than patients who receive ipilimumab. It should be noted that drug and administration costs are not included in the total costs given they are not calculated in a time-dependent manner.

Figure 5-38 and Figure 5-39 demonstrate that QALYs and life-years gained are higher for patients treated with T-VEC than for patients treated with ipilimumab. This is driven by improved PFS and OS associated with T-VEC. The incremental QALY gain and life-year gain is higher when using the modified Korn approach because of the lower PFS and OS

estimates for ipilimumab. The improved QALY gain and life-year gain accrued for T-VEC versus ipilimumab diminishes over time as fewer patients remain alive in the model and the OS curves converge.

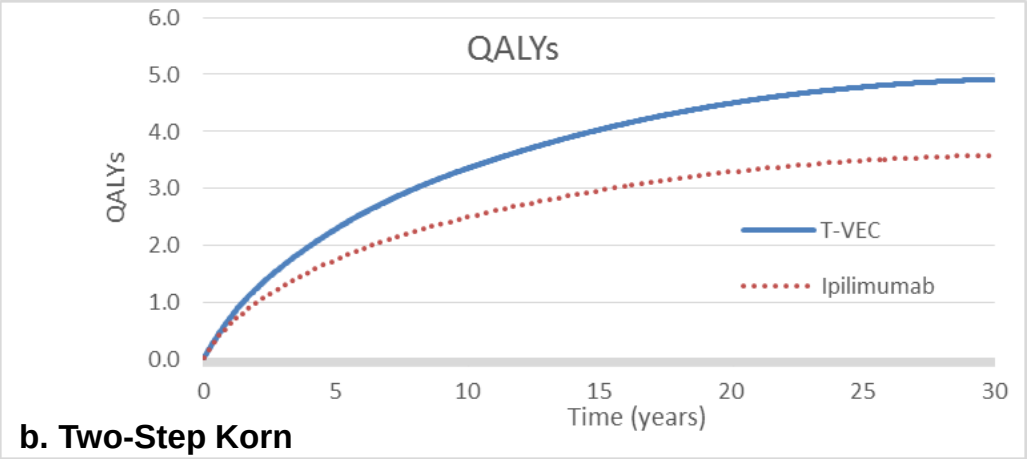
Figure 5-37: Cumulative costs over time for patients treated with either T-VEC or ipilimumab: modified Korn (a) and two-step Korn (b)

[redacted]

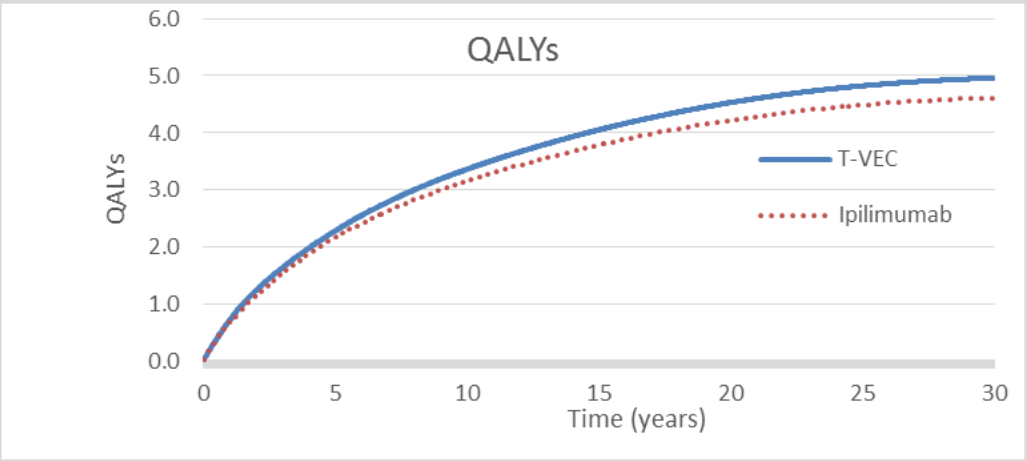
* Drug and administration costs are not included in the total beause they are not calculated in a time-dependent manner.

Figure 5-38: Cumulative QALYs over time for patients treated with either T-VEC or ipilimumab: modified Korn (a) and two-step Korn (b)

a. Modified Korn



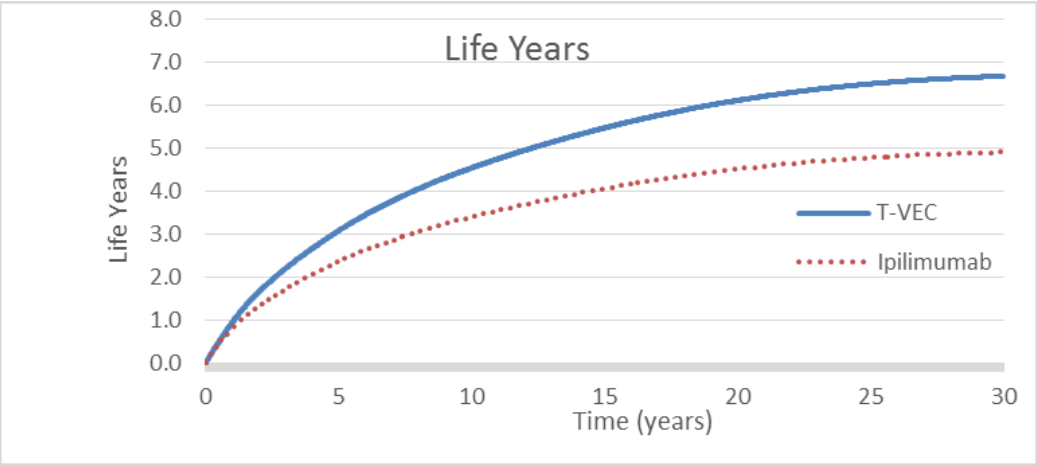
b. Two-Step Korn



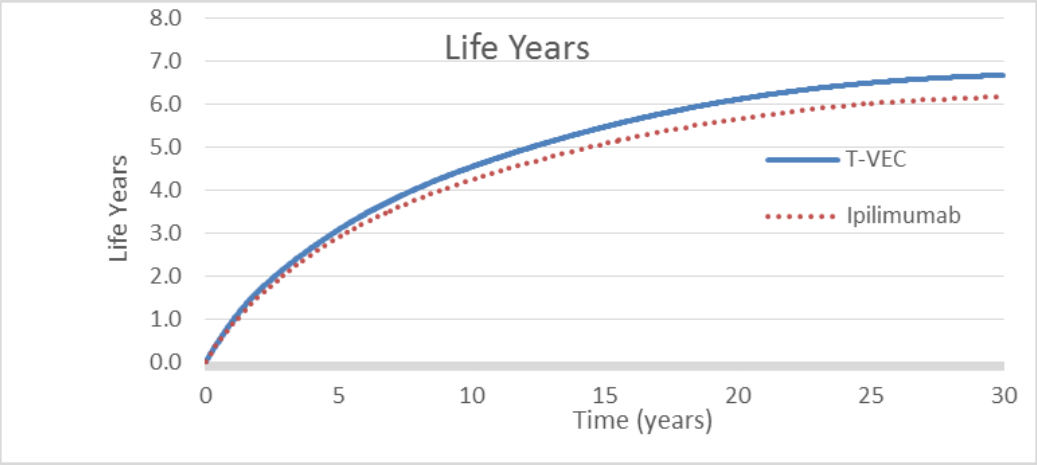
QALY, quality-adjusted life-year

Figure 5-39: Cumulative LYs over time for patients treated with either T-VEC or ipilimumab: modified Korn and two-step Korn

a. Modified Korn



b. Two-Step Korn



Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 5-28 illustrates the QALY gain by health state using the modified Korn and two-step Korn methods. Compared with patients treated with ipilimumab, in general, patients treated with T-VEC spend a longer time in both the pre- and post-progression health states; this is the case even when using the two-step Korn adjustment (worst case scenario for T-VEC) which ascribes the full interaction effect for ipilimumab in the T-VEC proposed licensed population. It is noteworthy that the increment is much larger for the pre-progression health state using the modified Korn method, whereas, the increment is larger for the post-progression health state using the two-step Korn method.

Table 5-28: Summary of QALY gain by health state

Health state	QALY: T-VEC	QALY: Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Pre-progression	3.25	2.06	1.19	1.19	89.13%
Post-progression	1.66	1.51	0.15	0.15	10.87%
Total	4.91	3.57	1.34	1.34	100%
Two-step Korn					
Pre-progression	3.61	3.55	0.06	0.06	16.80%
Post-progression	1.34	1.05	0.29	0.29	83.20%
Total	4.95	4.61	0.35	0.35	100%

QALY, quality-adjusted life year; T-VEC, talimogene laherparepvec

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 5-29 illustrates the disaggregated costs using the modified Korn and two-step Korn methods. Over a patient's lifetime, treatment with ipilimumab is expected to cost approximately £98,219. By comparison, treatment with T-VEC is expected to cost approximately [redacted] when the modified Korn adjustment method is used. When the two-step Korn adjustment method is used, ipilimumab and T-VEC are expected to cost approximately £96,035 and [redacted], respectively, over a patient's lifetime.

Table 5-29: Summary of costs and predicted resource use by health state

Health state	T-VEC	Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Pre-progression	[redacted]	£80,257	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	£17,963	[redacted]	[redacted]	[redacted]
Total	[redacted]	£98,219	[redacted]	[redacted]	[redacted]
Two-step Korn					
Pre-progression	[redacted]	£81,707	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	£14,328	[redacted]	[redacted]	[redacted]
Total	[redacted]	£96,035	[redacted]	[redacted]	[redacted]

T-VEC, talimogene laherparepvec

Adapted from: Pharmaceutical Benefits Advisory Committee (2008) guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 5-30 illustrates the predicted resource use by category of cost. T-VEC is associated with higher administration costs given the increased number of administrations compared to ipilimumab. In contrast, T-VEC with its favourable tolerability profile is associated with a lower cost of managing AEs compared to ipilimumab using both the modified Korn and two-step Korn methods.

Table 5-30: Summary of predicted resource use by category of cost

Item	T-VEC	Ipilimumab	Increment	Absolute increment	% absolute increment
Modified Korn					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.73%
Resource use	£35,561	£28,752	£6,810	£7,756	38.43%
AEs	£3	£118	–£115	£115	0.57%
Total	[redacted]	£98,219	[redacted]	[redacted]	[redacted]
Two-step Korn					
Treatment costs	[redacted]	£68,038	[redacted]	[redacted]	[redacted]
Administration costs	£5,092	£1,311	£3,780	£3,780	18.43%
Resource use	£34,419	£26,567	£7,852	£8,092	39.44%
AEs	£3	£118	–£115	£115	0.56%
Total	[redacted]	£96,035	[redacted]	[redacted]	[redacted]

AE, adverse event; T-VEC, talimogene laherparepvec

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 1.6 (List of model parameters).

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 5-31. These results are based on the anticipated list price for T-VEC and NHS list price for ipilimumab. In the modified Korn method, T-VEC is associated with an incremental cost of [redacted] and 1.24 incremental QALYs compared with ipilimumab. The ICER for the modified Korn analysis of [redacted] per QALY gained based on the probabilistic analysis remains close to the deterministic ICER of [redacted] per QALY gained

For the two-step Korn analysis, T-VEC is associated with an incremental cost of [redacted] and 0.24 incremental QALYs. The ICER for the two-step Korn analysis is [redacted] per QALY gained.

Table 5-31: Incremental cost-effectiveness results based on PSA

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs
Modified Korn					
T-VEC	[redacted]	4.79 (4.03-5.43)	[redacted]	1.24 (0.57-1.69)	[redacted]
Ipilimumab	£99,129 (£87,286-£112,458)	3.56 (3.11-3.97)			
Two-step Korn					
T-VEC	[redacted]	4.82 (4.06-5.39)	[redacted]	0.24 (-0.46-0.73)	[redacted]
Ipilimumab	£103,541 (£91,357-£116,535)	4.58 (4.19-4.95)			

The scatterplot of PSA iterations in Figure 5-40 and Figure 5-41 shows that there is little overlap in terms of the total costs and total QALYs for T-VEC and ipilimumab when using the modified Korn method and a considerable overlap when using the two-step Korn method. However, even in the worst case scenario (for T-VEC) using the two-step Korn method of estimating survival for ipilimumab in the anticipated T-VEC licensed population, the costs for T-VEC are generally slightly lower and the number of QALYs gained is generally slightly higher.

The cost-effectiveness acceptability curves show that when using the modified Korn adjustment (Figure 5-42) there is an approximately 98.39% chance of T-VEC being cost-effective when compared to ipilimumab at the £20,000 per QALY threshold (and 99.70% at a threshold of £30,000). When using the two-step Korn adjustment, which ascribes the best possible treatment effect to ipilimumab in the proposed T-VEC licensed population, the cost-effectiveness acceptability curve in Figure 5-43 shows that there is an approximately 80.02% chance of T-VEC being cost-effective when compared to ipilimumab at the £20,000 per QALY threshold (and 81.83% at a threshold of £30,000).

Figure 5-40: Scatterplot of PSA results (1,000 simulations; results discounted, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively) Modified Korn

[redacted]

Figure 5-41: Scatterplot of PSA results (1,000 simulations; results discounted, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively) Two-Step Korn

[redacted]

Figure 5-42: Cost-effectiveness acceptability curve (results discounted, with with anticipated and current NHS list prices for T-VEC and ipilimumab respectively): Modified Korn

[redacted]

Figure 5-43: Cost-effectiveness acceptability curve (results discounted, with with anticipated and current NHS list prices for T-VEC and ipilimumab respectively): Two-Step Korn

[redacted]

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted where modelling assumptions are changed one at a time for key variables. The following variables were increased and decreased by 20%:

- Duration of treatment
- Response rates
- Administration costs
- Discount rates
- Health state utility values

- Costs of terminal care

The results of the deterministic sensitivity analyses for the comparisons with ipilimumab are presented in Figure 5-44. These are presented with the anticipated and current NHS list prices for both T-VEC and ipilimumab respectively. Across both approaches (modified Korn method and two-step Korn method), the ICER was most sensitive to the duration of treatment for both T-VEC and ipilimumab. The rest of the variables had a minor impact on the estimated ICER.

Figure 5-44: Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, with anticipated and current NHS list prices for T-VEC and ipilimumab respectively)

a. Using Modified Korn Adjustment

[redacted]

b. Using Two-Step Korn Adjustment

[redacted]

Scenario analysis

In addition to conducting probabilistic and deterministic sensitivity analyses, alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions.

The following scenarios were evaluated:

- Varying the time horizon of the model: 10 years, 20 years and 25 years
- Varying the modelling approach for T-VEC dosing:
  - Include accelerated dosing and extension phase
  - Exclude accelerated dosing and extension phase
- Varying the modelling approach for IPI dosing
- Using alternative sources of utility estimates:
  - Beusterien study
  - TA 268
  - Amgen time trade study
- Applying alternative parametric curve fits:
  - Use log-normal and Weibull distributions as parametric curve fits for OS
  - Use log-normal and log-logistic distributions as parametric curve fits for PFS
- Applying alternative approach to modelling survival:
  - Use 2-part curve fit (Kaplan Meier+Regression) to model OS
  - Do not adjust long-term T-VEC PFS
- Varying resource use assumptions in terminal care:
  - TA319
- Varying resource use assumptions in routine treatment for non-progressive disease:
  - Costs of routine treatment with CR assumed to be zero for both T-VEC and IPI
  - Costs of routine treatment with CR, PR, SD, and PD reduced by 20%
  - Costs of routine treatment with CR, PR, SD, and PD increased by 20%

Table 5-32 reports the results of the scenario analyses. The scenario analysis showed that the cost-effectiveness of T-VEC is robust to the majority of potential sources of uncertainty. T-VEC was dominant (associated with lower costs and higher QALYs) for a number of the scenario analyses and remained cost-effective ([redacted] using the two-step Korn method) even in the scenario where a conservative dosing approach was evaluated (including both accelerated dosing and extension phase dosing).

Table 5-32: Results of the scenario analyses

Parameter	Base Case assumptions	Sensitivity Analysis	Modified Korn ICER		Two-Step Korn ICER	
			£/QALY	£/LYG	£/QALY	£/LYG
Base case result:			[redacted]	[redacted]	[redacted]	[redacted]
Varying the time horizon						
Time horizon	30 years	10 years	Dominant	Dominant	Dominant	Dominant
		20 years	[redacted]	[redacted]	[redacted]	[redacted]
		25 years	[redacted]	[redacted]	[redacted]	[redacted]
Varying the modelling approach for T-VEC dosing						
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Dominant	Dominant	Dominant	Dominant
Varying the modelling approach for IPI dosing						

IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	Dominant	Dominant	Dominant	Dominant
Varying the approach to modelling utilities						
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al.	[redacted]	[redacted]	[redacted]	[redacted]
		IPI 1 L (TA268)	[redacted]	[redacted]	[redacted]	[redacted]
		Amgen TTO study	[redacted]	[redacted]	[redacted]	[redacted]
Alternative parametric curve fits						
OS	Exponential	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS	Generalised gamma	Log-normal	[redacted]	[redacted]	Dominant	Dominant
		Log-logistic	[redacted]	[redacted]	Dominant	Dominant
Alternative approach to modelling survival						
OS	3-part curve fit	2-part curve fit	[redacted]	[redacted]	[redacted]	[redacted]
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	[redacted]	[redacted]	[redacted]
Varying resource use assumptions in terminal care						
Cost of terminal care	Amgen resource use study	TA319*	[redacted]	[redacted]	[redacted]	[redacted]
Varying resource use assumptions in routine treatment for non-progressive disease						
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR assumed to be zero for both T-VEC and IPI	[redacted]	[redacted]	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	[redacted]	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	[redacted]	[redacted]	[redacted]
BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; LYG, life-year gained; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; QALY, quality-adjusted life-year; SPC, summary of product characteristics; T-VEC, talimogene laherparepvec						

Summary of sensitivity analyses results

For the modified Korn adjustment, the probability of T-VEC being cost effective at a £20,000 per QALY threshold is 98.39% when compared to ipilimumab. Even in the worst case scenario for T-VEC using the two-step Korn adjustment, the probability of T-VEC being cost effective at a £20,000 per QALY threshold is 80.02% compared to ipilimumab.

One-way sensitivity analysis demonstrated that the duration of treatment for both ipilimumab and T-VEC had the greatest impact on the ICER for both the modified Korn method and the two-step Korn method.

Scenario analysis showed that the cost-effectiveness of T-VEC is robust to the majority of potential sources of uncertainty. The least favourable ICER, of [redacted] per QALY gained, was produced when T-VEC dosing included accelerated dosing and extension phase dosing using the two-step Korn method of adjustment.

5.9 Subgroup analysis

No subgroup analyses were considered in the cost-effectiveness analysis.

5.10 Validation

Validation of de novo cost-effectiveness analysis

The general model structure is consistent with metastatic melanoma models developed by comparator manufacturers that have been accepted by NICE. As outlined in Section 6.3, these elements were validated by key opinion leaders practising in the UK. The input of these clinicians and health economic experts has been used to inform the methods for survival analyses, dosing and application of adverse events. The opinions provided by these experts were also used in order to determine the model base case in terms of survival analysis using the modified Korn adjustment and the two-step Korn adjutsment.

Quality-control procedures for verification of input data and coding were performed by staff not involved in the model development. A checklist was used to ensure that the model generated accurate results and that these results are consistent with input data and robust to extreme values. The checks are documented in Appendix 1.9

As described in Table 5-27, the model predicted outcomes, both short and long term, for T-VEC in line with that observed in the pivotal clinical trial OPTiM. The Korn methodology (modified Korn adjustment and two-step Korn adjustment) was applied to estimate the survival of ipilimumab in the anticipated T-VEC licensed population. Given that the adjustment shifted upwards the survival curves for ipilimumab in this patient population with non-visceral metastatic disease, the comparison of the outputs estimated by the model based on the Korn methods of adjustment and the outputs from the clinical trials for ipilimumab which studied mostly patients with later stage metastatic disease are different.

5.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

No study assessing the cost-effectiveness of T-VEC was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

It was also not possible to compare the results of this submission to previous submissions given that the patient population assessed in this appraisal, non-visceral metastatic melanoma (Stage IIIB, IIIC and IVM1a), is different to the previous appraisals for melanoma which studied mostly patients in later stage metastatic disease.

Relevance of the economic evaluation for all patient groups

The target population included in the economic evaluation was consistent with the population eligible for T-VEC as per the proposed license. There is robust RCT data for T-VEC showing a clinically significant OS gain in its anticipated licensed population, i.e. the non-visceral metastatic disease (stage IIIB-IVM1a) population and consequently the evidence considered for T-VEC was in line with its proposed license.

Given the issue of broken networks and the heterogeneity of patient populations between T-VEC and comparator trials, it was not feasible to conduct an NMA. In addition, there is a dearth of data for the comparators in this patient population and consequently the clinical issue of the presence and the magnitude of interaction with treatment effect for the comparators in the T-VEC patient population are unknown. As there was no data for ipilimumab in the anticipated T-VEC licensed population (non-visceral metastatic melanoma, Stage IIIB/C, IVM1a), two alternative approaches using the modified Korn method and the two-step Korn method was used to estimate the survival for ipilimumab. The base case presents both approaches, the modified Korn method which assumes the absence of an interaction effect for ipilimumab in the anticipated T-VEC licensed population (best case) and the two-step Korn method which assumes the full interaction effect for ipilimumab based on uncertain clinical evidence (worst case). The likely ICER is expected to lie somewhere between the best and the worst case approaches.

Generalisability of the analysis to the clinical practice in England

The population included in the OPTiM trial, the main source of clinical evidence for T-VEC considered in the economic model, was generally comparable with the UK population. In terms of the treatment pathway, based on advice from clinical experts, patients with non-visceral metastatic disease are likely to receive an immunotherapy such as ipilimumab as first-line treatment, while BRAF inhibitors would be reserved patients with severe disease needing a rapid response. Therefore, the comparison of T-VEC in line with the expected license, versus ipilimumab is highly relevant to clinical practice.

Strengths and weaknesses of the evaluation

This is the first appraisal to evaluate the efficacy of a treatment for metastatic melanoma in the earlier stage of disease (i.e. non-visceral metastatic disease). While there is robust data for T-VEC it its proposed licensed population, there is a dearth of data for the comparators including ipilimumab. As such, different approaches to estimating survival for ipilimumab was used, one excluding the presence of any interaction with treatment effect (modified Korn

model) and another assuming the full interaction effect (two-step Korn model) It may be deemed that the “true” estimate of ipilimumab survival in non-visceral metastatic disease (stage IIIB-IVM1a), lies between the modified Korn adjustment which accounts only for prognostic variability and may not include any potential treatment interaction effect for ipilimumab and the two-step Korn adjustment which bestows the full treatment interaction effect based on a small subgroup of patients.

The model structure is based on overall survival and assumes that overall survival is a product of responses to both first and subsequent lines of treatment, as experienced in the RCTs. This structure was chosen because of the consistency between the costs and health outcomes. Although the use of subsequent therapies was balanced across treatment arms within the OPTiM trial and within the ipilimumab trial, the relative impact of subsequent therapies for T-VEC compared to ipilimumab is unclear and may be seen as a weakness of the evaluation.

Further analyses

There is genuine uncertainty around this important clinical issue of the presence of treatment interaction effect and the magnitude of the interaction effect for ipilimumab. The proposed confidential discount for T-VEC is a response to the uncertainties around this important clinical issue and mitigates any risk to the NHS. These uncertainties relate more to limitations of the evidence base of other comparators in T-VEC’s expected indication.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

Not applicable.

6.2 Number of people eligible for treatment in England

The patient population eligible for treatment with T-VEC has been estimated using the assumptions described in Table 6-1.

Table 6-1: With Stage IIIB, IIIC, IVM1a and unresectable disease - Assumptions

Assumption	Value		Source
Incident malignant melanoma population in 2011	13,348		Cancer Research UK incident malignant melanoma cases in 2011[23]
% Increase in incidence per annum	3.5%		NICE TA268[57]
Estimate of incident malignant melanoma population in 2015 (all stages	15,317		Calculated
Proportions of patients with stage IIIB – IVM1a disease	Stage IIIB/C	Stage IVM1a	Proportion of incident malignant melanoma patients with stage IIIB, IIIC, and IVM1a[22] disease
	3.6% (IIIB), 1.9% (IIIC)	3.8%	
Proportions of patients with injectable disease	73%	73%	Proportion of patients with lesions that are suitable for injection[80]
Proportions of patients diagnosed with metastatic or unresectable melanoma in whom chemotherapy/active treatment is suitable	70%	70%	NICE TA268[57]

The incident malignant melanoma population in England in 2011 was used to estimate the number of expected cases in 2015 by assuming an annual increase in incidence of 3.5%[57].

The number of patients eligible for treatment with T-VEC within its anticipated license (unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease) was subsequently estimated from the proportions of patients with stage IIIB – IVM1a disease with injectable lesions and suitability for active treatment. It is

estimated that 728 patients will be eligible for treatment in the first year, and the number of eligible patients from year 1 to year 5 (2015 – 2019) is presented in Table 6-2.

Table 6-2: Estimated eligible adult population with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease

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

6.3 Assumptions made about current treatment options and uptake of technologies

The main assumptions for estimating the number of patients eligible for treatment with T-VEC are:

- All patients are tested for BRAF V600 mutation status[57]
- 0% are treated through clinical trials[57]
- 3.5% incidence change rates per year[2]

As defined in the decision problem of this appraisal, the current treatment options in the patient population for which T-VEC is indicated are ipilimumab (NICE TA268[57], NICE TA319[2]), vemurafenib (NICE TA269[58]) and dabrafenib (NICE TA321[1]). All of these treatments have been recommended by NICE within their licensed indications as treatment options for the broader population of advanced (unresectable or metastatic) melanoma, however as described in Section 3.3, we consider ipilimumab to be the primary comparator in this appraisal.

It is noteworthy that although pembrolizumab is not defined as a relevant comparator in the scope of this appraisal, it is also likely to be a relevant treatment option in the patient population that T-VEC is indicated and as a conservative measure we have assumed a lower market share for T-VEC (Section 6.4) given the expected increase in the market share of pembrollizumab from ipilimumab.

6.4 Assumptions that were made about market share in England

The estimated market shares for T-VEC and the comparators defined in the scope of this appraisal are presented in Table 6-3 and it is assumed that:

- 48% of patients are BRAF V600 mutation positive[145] and 52% are BRAF V600 mutation negative
- T-VEC is used in both the BRAF V600 wild-type and BRAF V600 mutated populations
- Ipilimumab is used in both the BRAF V600 wild-type and BRAF V600 mutated populations
- Dabrafenib comprises nearly two-thirds of BRAF inhibitor use[80]
- The market shares above are applicable to the patient population with BRAF V600 positive mutation (48%) and BRAF wild type (52%)
- Pembrolizumab is not included since it is not a relevant comparator in this appraisal

It is assumed that the current market share for ipilimumab, vemurafenib and dabrafenib is 60%, 25% and 15% respectively, and that the uptake of T-VEC will increase over time as an alternative to the current treatments options. The market share assumptions for the BRAF inhibitors are based on European market research data[80] and the estimated market share for T-VEC is from Amgen internal forecasting. The absolute market shares and estimated number of patients eligible for treatment with T-VEC and the relevant comparators are summarised in Table 6-3 and Table 6-4 respectively.

Table 6-3: Estimated absolute market share of melanoma therapies in the T-VEC eligible patient population

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Current	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proposed	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		T-VEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6-4: Estimated numbers of patients eligible for treatment in the T-VEC eligible patient population

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Current	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Population	Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
			2015	2016	2017	2018	2019
Proposed	Stage IIIB/C, IVM1a	Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Dabrafenib‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		T-VEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Additional significant costs associated with treatment

Technology costs and other significant costs associated with administration of T-VEC are described in Section 5.3 to Section 5.6. The costs of monitoring have been included in addition to drug acquisition costs.

6.6 Unit costs

The costs considered in the budget impact analysis were derived from the economic model, as reported in Section 5.5 and includes:

- Acquisition costs
- Administration costs
- Adverse events costs
- Routine care costs
- Best supportive care costs

Given that ipilimumab is assumed to be the primary comparator in this submission, as a conservative measure, it was assumed that there will be no the impact of T-VEC on the BRAF inhibitors, and thus the costs of dabrafenib and vemurafenib have not been considered in the budget impact analysis.

6.7 Estimates of resource savings

The differential costs considered, both budget impact and budget savings, are incorporated as the incremental costs as calculated in the economic model.

6.8 Estimated budget impact on the NHS in England

The annual budget impact for the years 2015 to 2019 is provided in Table 6-5. As described in Section 6.7 the estimated budget impact includes the costs associated with drug acquisition and monitoring.

The introduction of T-VEC is anticipated to have a budget impact of [redacted] in 2015 and [redacted] in 2019 in adult patients with unresectable melanoma that is regionally or distantly metastatic with no visceral disease.

Table 6-5: Estimated budget impact over 5 years

Scenario	Costs	Year				
		Year 1	Year 2	Year 3	Year 4	Year 5
		2015	2016	2017	2018	2019

Scenario	Costs	Year				
		Year 1	Year 2	Year 3	Year 4	Year 5
		2015	2016	2017	2018	2019
Current	**Ipilimumab**					
	Drug costs*(£)	29,922,552	30,969,841	32,053,785	33,175,668	34,336,816
	Drug administration costs(£)	484,570	501,529	519,083	537,251	556,055
	AE costs (£)	51,973	53,792	55,675	57,623	59,640
	Non-progressive disease costs (routine care) (£)	1,071,784	1,109,296	1,148,122	1,188,306	1,229,897
	BSC costs(£)	941,878	974,844	1,008,963	1,044,277	1,080,827
	Total costs (£)	**32,472,756**	**33,609,303**	**34,785,628**	**36,003,125**	**37,263,235**
Future	**Ipilimumab**					
	Drug costs*(£)	28,426,424	21,162,725	18,698,042	19,352,473	20,029,810
	Drug administration costs(£)	460,341	342,712	302,798	313,396	324,365
	AE costs (£)	49,374	36,758	32,477	33,613	34,790
	Non-progressive disease costs (routine care) (£)	1,018,195	758,019	669,738	693,178	717,440
	BSC costs(£)	894,784	666,143	588,562	609,162	630,482
	Total costs (£)	**30,865,580**	**22,978,612**	**20,302,445**	**21,013,030**	**21,748,486**
	T-VEC					
	Drug costs*(£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Drug administration costs(£)	113,528	744,174	1,013,448	1,048,918	1,085,631
	AE costs (£)	63	412	561	581	601
	Non-progressive disease costs (routine care) (£)	53,589	351,277	478,384	495,127	512,457
	BSC costs(£)	36,838	241,472	328,847	340,357	352,270
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total current expenditure		**32,472,756**	**33,609,303**	**34,785,628**	**36,003,125**	**37,263,235**
Total future expenditure		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*All drug costs are based on anticipated list price for T-VEC and NHS list price for ipilimumab; BSC Best supportive care

6.9 Opportunities for resource savings or redirection of resources that it has not been possible to quantify

No other resource savings or redirection of resources is anticipated.

6.10 Main limitations within the budget impact analysis

Estimations of the total number of eligible patients treated with T-VEC were based on the estimated number of patients in Stage IIIB/C and IVM1a. Market share assumptions for the relevant comparators are based on limited evidence in the literature.

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