Talimogene laherparepvec for treating metastatic melanoma: an Evidence Review Group Perspective of a NICE Single Technology Appraisal

Short title: T-VEC for treating metastatic melanoma

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Abstract

The National Institute for Health and Care Excellence (NICE) invited the manufacturer (Amgen) of Talimogene laherparepvec (T-VEC) to submit clinical and cost effectiveness evidence for previously untreated advanced (unresectable or metastatic) melanoma as part of the Institute's Single Technology Appraisal process. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool was commissioned to act as the Evidence Review Group (ERG). This article presents a summary of the company's submission of T-VEC, the ERG review and the resulting NICE guidance (TA410), issued in September 2016. T-VEC is an oncolytic virus therapy granted a marketing authorization by the European Commission 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. Clinical evidence for T-VEC versus granulocyte-macrophage colony-stimulating factor (GM-CSF) was derived from the multinational, open-label randomized controlled OPTiM trial. In accordance with T-VEC's marketing authorization, the company's submission focused primarily on 249 patients with stage IIIB to stage IV/M1a disease who constituted 57% of the overall trial population (T-VEC, n=163 and GM-CSF, n=86). Results from analyses of durable response rate, objective response rate, time to treatment failure and overall survival all showed marked and statistically significant improvements for patients treated with T-VEC compared with those treated with GM-CSF. However, GM-CSF is not used to treat melanoma in clinical practice. It was not possible to compare treatment with T-VEC with an appropriate comparator using conventionally accepted methods due to the absence of comparative head-to-head data or trials with sufficient common comparators. Therefore, the company compared T-VEC with ipilimumab using what it described as modified Korn and two-step Korn methods. Results from these analyses suggested that treatment with T-VEC was at least as effective as treatment with ipilimumab. Using the discounted patient access scheme (PAS) price for T-VEC and list-price for ipilimumab, the company reported incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained. For the comparison of treatment with T-VEC versus

ipilimumab, the ICER per QALY gained was -£16,367 using the modified Korn method and -£60,271 using the two-step Korn method. The NICE Appraisal Committee (AC) agreed with the ERG that the company's methods for estimating clinical effectiveness of T-VEC versus ipilimumab were flawed and therefore produced unreliable results for modelling progression in stage IIIB to stage IVM1a melanoma. The AC concluded that the clinical and cost effectiveness of treatment with T-VEC compared with ipilimumab is unknown in patients with stage IIIB to stage IV/M1a disease. However, the AC considered that T-VEC may be a reasonable option for treating patients who are unsuitable for treatment with systemically administered immunotherapies (such as ipilimumab). T-VEC was therefore recommended by NICE as a treatment option for adults with unresectable, regionally or distantly metastatic (stage IIIB to stage IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if treatment with systemically administered immunotherapies is not suitable and the company provides T-VEC at the agreed discounted PAS price.

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Key Points

- For patients with unresectable, regionally or distantly metastatic (stage IIIB to stage IVM1a) melanoma, a population of patients for whom there are little data from other trials, the findings from the OPTiM trial demonstrate that Talimogene laherparepvec (T-VEC) is more efficacious than granulocyte-macrophage colony-stimulating factor (GM-CSF); however GM-CSF is not used to treat patients with melanoma in NHS clinical practice.
- It was not possible to compare T-VEC with a more relevant comparator (such as ipilimumab) using conventionally accepted methods and the methods utilized by the company instead (described as modified Korn and two-step Korn methods) were considered by the Evidence Review Group and Appraisal Committee (AC) to be methodologically flawed and therefore unsuitable for generating reliable estimates of clinical or cost effectiveness.
- T-VEC appears to have a better safety profile than systemically administered immunotherapy (particularly ipilimumab) although there are limited data to support the long-term safety of treatment with T-VEC.
- The AC considered that T-VEC may be a reasonable option for treating non-visceral metastatic disease that is unsuitable for treatment with systemically administered immunotherapies, providing T-VEC is made available at the discounted price presented in the patient access scheme.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England on a range of clinical and public health issues, including the appraisal of new health technologies. The NICE Single Technology Appraisal (STA) process is specifically designed for the appraisal of a single health technology for a single indication, where most of the relevant evidence lies with one manufacturer or sponsor and typically covers new technologies shortly after UK market authorisation is granted [1]. Within the STA process, the manufacturer or sponsor provides a written submission (alongside a decision-analytic model) that summarizes the company's estimate of the clinical effectiveness and cost effectiveness of the technology. An external independent organisation (typically, an academic group) known as the Evidence Review Group (ERG), provides a critique of the company's submission (the ERG report). Consultees, clinical specialists and patient representatives also provide additional information during the appraisal process.

Following a specification developed by NICE (the final scope), the NICE Appraisal Committee (AC) considers the company's submission, the ERG report and testimonies from experts and stakeholders in order to determine whether the technology represents a clinically and cost effective use of NHS resources. All stakeholders and the public have an opportunity to comment on the preliminary guidance issued by NICE the form of an Appraisal Consultation Document (ACD), after which the AC meets again to produce the final guidance (Final Appraisal determination [FAD]). The final guidance constitutes a legal obligation for NHS providers in England and Wales to provide a technology that is approved within its licensed indication [1].

This article presents a summary of the ERG report for the STA of Talimogene laherparepvec (T-VEC) for treating metastatic melanoma. Full details of all relevant appraisal documents

(including the appraisal scope, ERG report, company and consultee submissions, NICE guidance and comments on each of these) can be found on the NICE website [2].

2. The Decision Problem

Malignant melanoma is the most serious type of skin cancer. Melanoma can result in substantial impairment in health-related quality of life (HRQoL) in terms of physical and social functional domains [3] and facial or bodily disfigurement [4-6]. About 20% of patients present with stage III or IV disease. In the UK, five year survival rates range from 20% to 34% for patients with stage III disease and from 5% to 22% for patients with stage IV disease [7].

T-VEC is a genetically engineered herpes virus designed to replicate efficiently within tumours and to produce the immune stimulatory protein granulocyte-macrophage colony-stimulating factor (GM-CSF) in order to boost the body's immune system to protect the body from carcinogenesis and progression of cancer [8, 9]. T-VEC is administered by intra-lesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance. The European Commission granted a marketing authorisation for T-VEC in December 2015 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 [10]. Throughout the company's submission (and this paper) this type of melanoma is referred to as non-visceral metastatic disease.

Ipilimumab and, for patients with B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations, vemurafenib and dabrafenib were considered as comparators to T-VEC by the company. This is because, at the time of the company's submission to NICE in November 2015, these were the only treatments recommended by NICE for the treatment of malignant melanoma [11-14]. Pembrolizumab was recommended by NICE for treating advanced melanoma after disease progression with ipilimumab in October 2015 [15] (and for ipilimumab

naive patients in December 2015 [16]), but was considered beyond the scope of the current appraisal since the final scope had been issued by NICE in September 2015.

3. Independent Evidence Review Group Report

The evidence provided by the company comprises an initial submission, a cost effectiveness model and the company's response to the ERG's clarification requests. The ERG report [17] is a summary and critical review of the evidence for the clinical and cost effectiveness of the technology provided by the company. The aims of the report are:

- To assess whether the evidence submitted by the company conforms to the methodological guidelines issued by NICE
- To assess whether the company's interpretation and analysis of the evidence are appropriate
- To indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform the development of NICE guidance.

In addition to providing this detailed critique, the ERG modified a number of key assumptions and parameters within the company's economic model. The purpose of these changes was to explore the robustness of the company's results.

3.1 Clinical Evidence

The company conducted a systematic literature review and concluded that only the OPTiM trial [18] included T-VEC as an intervention or comparator. An additional nine randomized controlled trials (RCTs) [19-27] which evaluated ipilimumab, vemurafenib or dabrafenib were considered for inclusion in a network meta-analysis (NMA).

The OPTiM trial was a multinational, open-label RCT that was designed to compare treatment with T-VEC injected directly into lesions with subcutaneous GM-CSF. Patients with stage IIIB to stage IVM1c disease 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) defined as partial response or complete response that lasted continuously for over 6 months.

Subgroup analyses of DRR and the secondary outcomes of objective response rate (ORR) and overall survival (OS) by different stages of disease (stage IIIB to stage IIIC, stage IVM1a, stage IVM1b and stage IVM1c) were pre-specified in the trial protocol. However, the information provided in the company's submission related, primarily, to patients with non-visceral metastatic disease, i.e. the subgroups of patients with stage IIIB to stage IIIC combined with those with stage IVM1a disease who made up 57% of the overall trial population (n=249; T-VEC, n=163 and GM-CSF, n=86). Baseline characteristics for the overall trial population and for patients with non-visceral metastatic disease were similar and were generally balanced across treatment arms. The results from the analyses of DRR, ORR, time to treatment failure (TTF) and OS showed that there were marked, and statistically significant, improvements across all these outcomes for patients treated with T-VEC compared to patients treated with GM-CSF (Table 1).

In the OPTiM trial [18], the incidence of all types of adverse events (AEs) was higher for patients treated with T-VEC compared with patients receiving GM-CSF (Table 2). Treatment-related AEs experienced by patients treated with T-VEC were reported as being generally mild and reversible. For patients with non-visceral metastatic disease, the most common (>20%) AEs reported in the T-VEC arm of the trial were chills (49.1%), fatigue (44.8%), pyrexia (38.0%), influenza like illness (33.7%), injection site pain (28.2%) and nausea (25.2%) and, in the GM-CSF arm, fatigue (31.6%). Cellulitis was the only Grade 3 or higher AE occurring in >2% of patients with non-visceral metastatic disease treated with T-VEC (2.1%). The only fatal

AE reported for patients with non-visceral metastatic disease was considered unrelated to treatment with T-VEC.

The company only presented HRQoL data for patients with non-visceral metastatic disease from the OPTiM trial. Results were reported to be statistically significant in favour of T-VEC for six of 11 measures on the Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM) questionnaire.

As GM-CSF was not a relevant comparator, the company had planned to construct a NMA to allow the clinical effectiveness of T-VEC relative to the comparators listed in the NICE scope to be (indirectly) estimated. However, a valid network of evidence could not be established because of a lack of comparative head-to-head data or trials with sufficient common comparators. It was further noted that the proportion of patients in the non-visceral metastatic disease subgroup varied widely between trials, ranging from 57% in the OPTiM trial, to much lower percentages in the relevant comparator arms of the trials: ipilimumab (11% [21] to 17% [27]), vemurafenib (18% [19] to 23% [22]), and dabrafenib (16% [24] to 20% [20]). The company therefore considered alternative methods for obtaining indirect estimates of effect, eventually choosing to use two approaches: the modified Korn method (which had been developed by the manufacturer of ipilimumab for use in the STA of ipilimumab for previously untreated advanced melanoma [11]); and the two-step Korn method, which the company devised for this current STA. Both approaches were modifications of a model developed by Korn et al in 2008 [28] and both were used to adjust the survival curves (OS and progression-free survival [PFS], considered to be a proxy for TTF) of ipilimumab. However, the company did not attempt to adjust the survival curves of patients receiving vemurafenib or dabrafenib since the trials included in the meta-analysis which forms the basis for the original Korn model [28] did not differentiate patients by BRAF status. Therefore, the company only compared T-VEC with ipilimumab.

Data were collected for patients treated with ipilimumab from two RCTs: (i) the MDX010-20 three-armed trial [21] in which patients received ipilimumab plus glycoprotein 100 peptide vaccine (gp100), gp100 alone or ipilimumab alone; (ii) the CA184-024 trial [27] which was designed to compare treatment with ipilimumab in combination with the chemotherapy drug dacarbazine versus placebo plus dacarbazine. Dacarbazine and gp100 were assumed, by the company, to be clinically ineffective treatments and hence all patients who received ipilimumab combination therapy were considered to have effectively received ipilimumab alone. Use of the modified Korn and two-step Korn methods was intended by the company to correct for differences in patient characteristics so that patients in the ipilimumab trials [21, 27] would be comparable to patients with non-visceral metastatic melanoma in the OPTiM trial. The two-step Korn method also included an adjustment for a possible treatment-subgroup interaction effect between ipilimumab and disease stage (i.e. it assumes ipilimumab has a greater effect in earlier stage disease). The additional adjustment was considered to be equivalent to the hazard ratio (HR) reported for the subgroup analysis of OS in the MDX010-20 trial [21] (HR=0.47). This estimate was more conservative than the HR (0.83) calculated for a similar subgroup analysis of OS in the CA184-024 trial [27]. Results using the modified Korn method were found by the company to suggest T-VEC to be superior to ipilimumab in terms of median OS and PFS, whereas results using the two-step Korn method were found to suggest that T-VEC is at least comparable to ipilimumab for these two outcomes (Table 3).

3.2 Critique of the Clinical Evidence and Interpretation

The ERG considered additional comparators may have been relevant to this STA. In particular, the ERG considered that, at the time of the appraisal, the most appropriate comparator to T-VEC was likely to be pembrolizumab as this had only recently been recommended for treating melanoma by NICE [15]. The ERG, however, recognised that pembrolizumab was not licensed or used in the NHS at the time the NICE scope was finalised.

In its critique, the ERG considered that isolated limb perfusion or electrochemotherapy may also have been relevant comparators for a minority of patients for whom a systemically administered immunotherapy (such as ipilimumab, pembrolizumab or nivolumab) would not be the preferred treatment of choice,.

Overall, the ERG considered patients with non-visceral metastatic melanoma who participated in the OPTiM trial were representative of patients suitable for treatment with T-VEC in NHS clinical practice. However, the ERG cautioned that where patients had received previous treatment in the OPTiM trial (53.4% of patients in the overall trial population), the type of treatment received differed from treatments given to patients with metastatic melanoma in clinical practice today. Thus, it is unclear if the effectiveness results for the previously treated population in the OPTiM trial could be replicated in NHS clinical practice in England.

A number of potential sources of bias in the OPTiM trial were noted by the ERG (see Box 1). However, the ERG considered that it was unlikely that bias alone could explain the large differences in outcomes reported between arms in the subgroup of patients with non-visceral metastatic disease.

The ERG noted that a substantial proportion of patients in the GM-CSF arm did not fully complete the questionnaires. Therefore the ERG considered that the HRQoL findings should be interpreted with caution.

The ERG agreed with the company that a NMA could not be conducted due to the absence of a common comparator. The ERG commended the company's attempts to compare T-VEC with a relevant comparator through the use of the two novel methods. However, the ERG had many concerns regarding the use of the modified Korn and two-step Korn methods that were used by the company to facilitate a comparison of the effectiveness of treatment with T-VEC versus ipilimumab. The ERG noted that the purpose of the original Korn model [28] was to

develop benchmarks for OS and PFS to help clinical researchers design new phase II clinical trials of potentially promising treatments for patients with metastatic melanoma. Furthermore, the original method was developed using data in which the majority of people had stage IV melanoma. The ERG also noted that, in the original Korn model, the authors developed separate models for OS and PFS, each with different variables [28]. Where the same variables were present in both the OS and PFS models (Eastern Cooperative Oncology Group performance status and sex), notably different coefficient values were assigned to these factors, thereby giving different weight to these variables. The modified Korn and the two-step Korn methods included an adjustment for elevated lactate dehydrogenase (LDH) which is not a relevant factor for people with stage IIIB to stage IVM1a disease. The ERG considered that including LDH had the effect of reducing the size of the coefficients associated with other adjustment factors and thereby improved the relative efficacy of T-VEC. Since the effectiveness of ipilimumab can vary significantly by stage of disease, the company's attempts to correct for case-mix imbalance by using the two-step model was likely to further compound these problems. Finally, the ERG noted that pooling ipilimumab data from the ipilimumab monotherapy and ipilimumab in combination with gp100 or dacarbazine arms of two published trials of ipilimumab [21, 27] required three key assumptions: (i) dacarbazine and gp100 are both ineffective (ii) survival patterns are equivalent regardless of whether ipilimumab is administered as a first-line or as a subsequent line of therapy and (iii) censoring occurs at a constant rate within each (arbitrary) time period. The ERG did not consider all of these assumptions could be substantiated. Thus, taking all of the issues into consideration, the ERG concluded it was inappropriate to use the modified Korn or two-step Korn methods to attempt to correct for differences in prognostic factors for patients with stage IIIB to stage IVM1a disease.

In addition, the ERG noted that even in the small proportions of patients with non-visceral metastatic disease in the two ipilimumab trials [21, 27], not all of these patients would necessarily have had injectable melanoma. Therefore, the characteristics of patients with non-

visceral metastatic disease in the trials of ipilimumab may have differed from those of patients with non-visceral metastatic melanoma in the OPTiM trial.

The ERG agreed that treatment with T-VEC compares favourably in terms of safety when compared with ipilimumab, BRAF inhibitors and also with pembrolizumab. However, the ERG noted that the EMA [29] has highlighted that the data on long-term exposure to T-VEC are currently limited.

3.3 Cost effectiveness evidence

To allow the cost effectiveness of T-VEC to be compared with ipilimumab, the company developed a de novo partitioned survival model. The perspective was that of the NHS and the time horizon was lifetime (30 years). The cycle length was 1 week and a half-cycle correction was applied. As recommended by NICE, costs and outcomes were discounted at 3.5% per annum. Outcomes were measured in quality adjusted life years (QALYs). Variants of this model structure have been used in a number of previous STAs that have considered the cost effectiveness of treatments for patients with metastatic melanoma [11, 13, 14].

The model comprised three mutually exclusive health states: non-progressive disease (including complete response, partial response and stable disease), progressive disease (which equated to TTF based on OPTiM trial data for patients treated with T-VEC) and death. All patients entered the model in the non-progressive disease state. Transition to another state depended on response to treatment; PFS and OS for patients receiving T-VEC were based on OPTiM trial data and for patients treated with ipilimumab, PFS and OS were derived from the modified Korn and two-step Korn methods. The company applied different parametric curves to extrapolate PFS and OS and concluded that the generalized gamma distribution provided the best fit to the data for T-VEC and ipilimumab. The modelling of OS for patients

treated with ipilimumab used a multi-phase approach, but with cut-points implemented at different times to those used to estimate OS for patients treated with T-VEC

Two different OS projections were developed for ipilimumab patients, depending on whether the modified Korn or the two-step Korn method was used to adjust for differences in baseline characteristics between the two relevant trials of ipilimumab [21, 27] and the OPTiM trial.

Health state utility values from a previous NICE appraisal of dabrafenib for the treatment of unresectable or metastatic BRAF V600 mutation positive melanoma [14] were used in the model. Disutility values associated with AEs of Grade 3 or more, with an incidence of 2% or more, were obtained from a proprietary study [30] commissioned by the company in which respondents were asked to value different states associated with advanced melanoma. Resource use and costs associated with treatment and disease progression were estimated based on information collected in the company's resource utilisation study [31], published sources [11-13, 15, 32-35] and the views of clinical experts.

For the comparison of T-VEC versus ipilimumab, using the modified Korn and two-step Korn methods, the company reported that treatment with T-VEC was associated with 1.34 and 0.35 additional QALYs respectively. The incremental cost effectiveness ratios are considered to be commercial in confidence in the company's submission. The company also carried out a range of one-way deterministic sensitivity analyses which showed that the most influential variables were the duration of treatment and the prices of the two drugs. The results of the company's probabilistic sensitivity analysis (PSA) showed that using the modified Korn method, compared with ipilimumab, the probability of T-VEC being cost effective was 98.4% and 99.7% at thresholds of £20,000 and £30,000 per QALY gained, respectively. Using the two-step Korn method, these probabilities were reduced to 80.0% and 81.8% respectively.

Since a confidential patient access scheme (PAS) exists for ipilimumab (meaning that it is available to NHS patients in England at an undisclosed discounted price) the company also

calculated ICERs per QALY gained for a range of discounts for ipilimumab. The company's results showed that in analyses that used the modified Korn and two-step Korn methods to model the efficacy of ipilimumab, the ICER remained below a threshold of £30,000 per QALY gained when discounts of ≤55% or ≤10% respectively were assumed.

The Department of Health and the company have agreed that T-VEC will be available to the NHS with a PAS. The size of the discounted price of T-VEC is commercial in confidence. Using the PAS price for T-VEC and list-price for ipilimumab, the ICER per QALY gained for a comparison of the cost effectiveness of treatment with T-VEC versus ipilimumab was -£16,367 using the modified Korn method and -£60,271 using the two-step Korn method.

3.4 Critique of the Cost effectiveness Evidence and Interpretation

As NICE had recently recommended pembrolizumab for both first-line [16] and second-line [15] treatment of patients with metastatic malignant melanoma, the ERG considered that clinicians' first choice systemic treatment will likely shift away from ipilimumab towards pembrolizumab. Thus a comparison of T-VEC with ipilimumab, may only be relevant to usual clinical practice in England for a limited period of time.

As documented in the ERG report, the ERG also had concerns with the company's approach to modelling survival using the modified Korn and two-step Korn methods as previously described (section 3.2). A number of issues with the company's multi-phase approach to extrapolating survival were identified by the ERG. For example, in the first phase of the model, the exponential trend used by the company to project OS for patients treated with T-VEC deviates markedly from the final recorded OPTiM trial data resulting in a higher OS estimate for T-VEC by 49% to 59%. Also, in the second phase of modelling OS, the company used the published results of the analyses of patient registry data on which the American Joint Committee on Cancer (AJCC) [36] staging classification was based. For patients with stage I,

stage II and stage III disease, the AJCC survival trends provide results from the date of diagnosis, whilst for patients with stage IV disease trends are recorded from the time of identification of first distant metastases. This means the estimates used in the company model mix patients at very different times in their disease progression (from 0 to >20 years after first diagnosis). Furthermore, the data on which the AJCC analyses were performed were gathered prior to the current era of novel immunological treatments and may be unrealistic as newer treatments have significantly altered the longer term survival for many patients; hence, the company's model implied little or no benefit after 5 years. Moreover, the ERG highlighted a sudden increase in the mortality rate at the junction between the first and second phases (after 270 weeks [62.1 months]) in the company's model, which the ERG considered to be an arbitrary effect with no clinical justification. Finally, for phase 3 (after 10 years), UK life table mortality rates [37] were applied within the company model without adjustment, other than for age and sex. Thus, the mortality risk for long-term survivors of malignant melanoma became the same as that for the general population, which implied that, at this time point, the cohort of long-term survivors was suddenly cured. The ERG was not aware of any evidence to support such an effect. To remedy these issues, the ERG carried out a curve-fitting exercise and found that in the T-VEC arm, a 2-part exponential model closely followed the trial OS data from 9 months (about 270 days) until the last recorded death at 47 months (about 1,400 days).

Given the serious problems identified by the ERG relating to the construction of an ipilimumab comparator for use in the company model, the ERG did not consider that any estimates of the cost effectiveness of T-VEC compared with ipilimumab for patients with non-visceral metastatic disease would be sufficiently reliable to inform decision-making. Using different assumptions, widely differing estimated ICERs can be obtained, from T-VEC appearing to be dominant compared with ipilimumab (better outcomes at lower cost) to T-VEC appearing to be dominated by ipilimumab (poorer outcomes at higher cost). This the ERG considered that quoting any specific unreliable ICERs would be potentially misleading.

3.5 Conclusions of the ERG report

The ERG considered that, given the issues of concern regarding the use of the modified Korn and two-step Korn methods, the relative clinical effectiveness of T-VEC compared with ipilimumab is unknown. T-VEC does, however, appear to have a better safety profile than systemically administered immunotherapy (particularly ipilimumab), vemurafenib or dabrafenib although there are limited data to support the long-term safety of treatment with T-VEC.

Given the serious problems identified by the ERG relating to the construction of an ipilimumab comparator for use in the company's model, the ERG did not consider that any estimates of the cost effectiveness of T-VEC compared with ipilimumab would be reliable. Furthermore, the ERG considered that serious issues relating to the methods employed by the company to project long-term survival further undermined the reliability of the company's cost effectiveness results.

4. National Institute for Health and Care Excellence Guidance

The AC reviewed the evidence available on the clinical and cost effectiveness of T-VEC alongside expert testimony from a clinical experts and patient representatives.

4.1 Preliminary guidance

At the first AC meeting, the AC considered that the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for people with metastatic melanoma. The AC agreed that T-VEC presented an innovative treatment approach. The clinical experts considered the main benefits of T-VEC to be that the method of administration is acceptable to patients and that it has an improved safety profile compared

to currently available treatments, particularly ipilimumab. The AC considered ipilimumab to be the most appropriate comparator since other systemically administered immunotherapies (pembrolizumab and nivolumab) were beyond the scope of the current appraisal. The AC concluded that the evidence presented by the company was insufficient to draw any firm conclusions about the clinical effectiveness of T-VEC compared with relevant comparators in patients with non-visceral disease. Moreover, from the evidence presented, the AC could not be confident that T-VEC had been convincingly shown to be at least as effective as ipilimumab in this patient group. The AC did consider that T-VEC may be a reasonable treatment option for patients with non-visceral disease for whom systemically administered immunotherapies were unsuitable. However, the AC was not presented with evidence as to how this group of patients could be defined.

While the AC accepted the basic structure of the company's economic model, it questioned some of the model inputs. In particular, the AC considered that the original Korn method was not designed for modelling progression in stage IIIB to stage IVM1a melanoma. It agreed with the ERG that the modifications made to the original Korn method to derive the modified Korn and two-step Korn methods further compounded the underlying issues that the ERG had identified with the original Korn method. The lack of suitable effectiveness inputs in the economic model prevented the AC from calculating a plausible estimate of cost effectiveness.

On the evidence available, the AC could not be confident that T-VEC had been convincingly shown to be at least as clinically effective as ipilimumab. The AC concluded that it could not recommend T-VEC within its marketing authorization for the treatment of non-visceral metastatic disease as it was not possible to establish a reliable estimate of the effectiveness of treatment with T-VEC compared with systemically administered immunotherapies currently used in NHS clinical practice. The draft Appraisal Consultation Document (ACD) was issued for consultation and interested parties had an opportunity to comment on the draft.

4.2 Company response to the Appraisal Consultation Document (ACD)

Following the first AC meeting, the company submitted additional analyses in response to the ACD. These were intended to address uncertainty around the relative clinical effectiveness of T-VEC compared with ipilimumab. Additional submitted evidence included the use of the modified Korn and two-step Korn methods to adjust the effectiveness of ipilimumab data in the whole OPTiM trial population (i.e. to include patients with stage IVM1b and stage IV1c disease as well as those with stage IIIB to stage IVM1a disease). The company stated that the results of this analysis suggest that treatment with T-VEC is at least as effective as ipilimumab. The company also submitted a 'naïve' indirect comparison of T-VEC with ipilimumab in which GM-CSF, dacarbazine and gp100 were assumed to be of equal efficacy in the treatment of metastatic melanoma. The company argued that this analysis also shows that treatment with T-VEC is at least as effective as ipilimumab.

Regarding cost effectiveness, the company questioned the validity of the ERG's method for extrapolating OS data in the T-VEC arm. In particular, the company highlighted that 24% of patients in the T-VEC arm of the OPTiM trial were alive at 47 months and remained so at 60 months. The company therefore argued that the entire Kaplan-Meier curve provided a more relevant basis for extrapolation than the period between 9 and 47 months used by the ERG. The company also highlighted that the ERG had estimated the mean OS for T-VEC to be 73 months based on their extrapolation instead of 108.5 months based on the company method but left unchanged the mean OS for ipilimumab (at 100 months using the company method). The company argued that the ERG should therefore have applied the same method for extrapolating data to patients treated with ipilimumab as to patients treated with T-VEC.

The company also presented analyses comparing treatment with T-VEC versus dacarbazine and best supportive care (BSC) by assuming that dacarbazine and BSC are of equal efficacy

to GM-CSF. These analyses resulted in ICERs of £23,900 and £24,100 per QALY gained respectively. These ICERs were noted by the company to be substantially lower than the ICERs per QALY gained reported in previous NICE guidance [11, 12] which considered the comparisons of treatment with ipilimumab versus dacarbazine for previously untreated patients (£47,900) and for ipilimumab versus BSC for previously treated patients (£42,200).

4.3 ERG critique of the response submitted by the company to the ACD consultation

The ERG considered that the additional analyses using the modified Korn and two-step Korn methods did not address the underlying methodological concern that the models had not been calibrated against patient-level data from trials of ipilimumab in a population that was similar to the OPTIM trial population (see section 3.2). Nor did the ERG consider that the company's 'naïve' indirect comparison was a reliable method of establishing the relative effectiveness of these agents.

Regarding the extrapolation of OS data, the ERG did not consider the company's method of extrapolating survival beyond 47 months to be clinically plausible. This is because the addition of extra censored data points beyond the last recorded death would implicitly assume that, after the last death, the mortality risk is actually zero (i.e. 24% of patients benefit from up to 15 months of immunity from death from any cause) and therefore the model assumes a patient who is still alive can be expected to remain indefinitely free of the risk of death (from any cause, not just melanoma).

Finally, in relation to the comparison of T-VEC with dacarbazine and BSC, the ERG made several amendments to the company's model. These included employing ERG preferred methods for extrapolating OS and PFS for T-VEC, applying annual discounting, using utility values from a study [30] commissioned by the company (including terminal disutility) and

applying a mid-cycle correction for the estimation of outcomes and costs. The net effect of applying all of the model amendments was to produce a modest increase in the size of the estimated ICER per QALY gained. The ICER per QALY gained for T-VEC versus dacarbazine was £29,303 and the ICER per QALY gained for T-VEC versus BSC was £30,427.

4.4 Final guidance

The AC concluded that there is no methodologically valid way of comparing treatment with T-VEC with ipilimumab for patients with stage IIIB to IVM1a melanoma. The AC also considered whether there was a subgroup of patients for whom treatment with T-VEC would be particularly beneficial. In particular, the AC considered whether there was a group of patients for whom T-VEC might be the only effective option, such as those for whom systemically administered immunotherapies were contraindicated. In response to consultation following the AC's initial decision, a clinical expert highlighted that there were people for whom systemically administered immunotherapies are not suitable and for whom there is currently no other effective treatment options. It was noted that cost effective analyses presented by the company comparing treatment with T-VEC with treatment with dacarbazine or BSC did not specifically relate to this group of patients. However, the AC was satisfied that these analyses provided an indication of the cost effectiveness of T-VEC.

In conclusion, the AC concluded that the clinical effectiveness of T-VEC compared with ipilimumab was so uncertain that it was it was not possible to establish whether T-VEC was a cost effective use of NHS resources. However, the AC considered that T-VEC may be a reasonable option for treating non-visceral metastatic disease that is unsuitable for treatment with systemically administered immunotherapies. Therefore, T-VEC was recommended by NICE as a treatment option for adults with unresectable, regionally or distantly metastatic (stage IIIB to stage IVM1a) melanoma that has not spread to bone, brain, lung or other internal

organs, only if treatment with systemically administered immunotherapies is not suitable and the company provides T-VEC as per the discount agreed in the PAS.

5. Conclusion

The key clinical and cost effectiveness issues in this appraisal arose from the difficulty in comparing treatment with T-VEC versus ipilimumab primarily because of the lack of a direct comparison of T-VEC with a relevant comparator and the lack of a common comparator to enable a NMA to be conducted. Furthermore, systemically administered immunotherapies have not been studied solely in the patient population for which T-VEC is licensed (patients with stage IIIB to stage IVM1a melanoma). Therefore, the true clinical benefit of treatment with T-VEC compared with ipilimumab (or any other systemically administered immunotherapy) could not be determined from currently available evidence. As a result, the AC concluded that T-VEC could only be recommended as a treatment option for patients for whom systemically administered immunotherapies are not suitable.

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Nigel Fleeman: Project lead, drafted clinical results section and supervised the final report

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Marty Richardson: Critical appraisal of the statistical evidence

Ashma Krishan: Critical appraisal of the statistical evidence

Angela Boland: Critical appraisal of the clinical and economic evidence

Sophie Beale: Critical appraisal of the clinical and economic evidence

Angela Stainthorpe: Critical appraisal of the economic evidence and checking and validation of the economic model

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Lindsay Banks: Critical appraisal of the submission

Miranda Payne: Clinical advice and critical appraisal of the clinical sections of the company's submission

All authors read and commented on draft versions of this paper

Competing interests

Within the last 3 years Miranda Payne has received fees for speaking for advisor board membership from GlaxoSmithKline, Novartis, Merck Sharp & Dohme and Bristol-Myers Squibb and support with travel to conferences from Bristol-Myers Squibb and GlaxoSmithKline. None of the other authors have any competing interests.

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Tables, figures and boxes

Table 1 Summary of key efficacy and safety results in the OPTiM trial [18]

Outcome	Patients with non-visceral metastatic disease		Overall trial population[a]	
	T-VEC (n=163)	GM-CSF (n=86)	T-VEC (n=295)	GM-CSF (n=141)
DRR by EAC assessment (%)[b]	25.2	1.2	16.3	2.1
Unadjusted odds ratio (95% confidence interval)	28.6 (3.9 to 211.5)		8.9 (2.7 to 29.2)	
P-value	<0.0001		<0.0001	
ORR by EAC assessment (%)[b]	40.5	2.3	26.4	5.7
P-value	<0.0001		<0.0001	
Median TTF by investigator assessment (months)[c]	13.1	3.3	8.1	2.9
Hazard ratio (95% confidence interval)	0.28 (0.20 to 0.40)		0.43 (0.33 to 0.56)	
P-value	<0.0001		<0.0001	
Median OS (months)[c]	46.8	21.5	23.3	18.9
Hazard ratio (95% confidence interval)	0.56 (0.40 to 0.79)		0.79 (0.62 to 1.00)	
P-value	0.0008		0.0494	

DRR durable response rate, *EAC* Endpoint Assessment Committee, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *ORR* overall response rate, *OS* overall survival, *TTF* time to treatment failure, *T-VEC* talimogene laherparepvec
[a] Intention-to-treat population, i.e. all patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received
[b] Primary data-cut
[c] Final data-cut
Source: Table 10 of Evidence Review Group report [17] (Crown copyright)

Table 2 Summary of safety profiles of T-VEC and GM-CSF in the OPTiM trial [18]

Type of safety concern	Patients with each type of AE (%)			
	Non-visceral metastatic disease		Overall trial population[a]	
	T-VEC (n=163)	GM-CSF (n=76)	T-VEC (n=292)	GM-CSF (n=127)
Treatment emergent AE	99	93	99	95
Treatment-related AEs	93	79	93	80
Treatment emergent SAE	20	13	26	13
Treatment-related SAE	6	0	7	0
Treatment emergent AE leading to discontinuation	9	7	10	6
Fatal AEs on study	1	0	3	2

AE adverse event, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *SAE* serious adverse event, *T-VEC* talimogene laherparepvec
[a] Safety population, i.e. patients who received at least one dose of T-VEC or GM-CSF (per-protocol analysis)
Source: adapted from Table 13 of Evidence Review Group report [17] (Crown copyright)

Table 3 Median and mean overall survival and progression-free survival for patients with non-visceral metastatic disease treated with T-VEC and ipilimumab

Outcome / trial arm	T-VEC	Ipilimumab (pooled)[a]
Median OS		
Unadjusted, modified Korn	46.8	10.9
Adjusted, modified Korn (95% prediction interval)	–	21.3 (14.6 to NR)
Unadjusted, two-step Korn	46.8	10.9
Adjusted, two-step Korn (95% prediction interval)	–	NR (27.0 to NR)
Mean OS[b]		
Unadjusted, modified Korn	36.9	19.5
Adjusted, modified Korn (95% prediction interval)	–	29.2 (23.8 to 34.6)
Unadjusted, two-step Korn	33.5	18.0
Adjusted, two-step Korn (95% prediction interval)	–	32.3 (28.1 to 35.8)
Median PFS		
Unadjusted, modified Korn	13.1	2.8
Adjusted, modified Korn	–	5.3
Unadjusted, two-step Korn	13.1	2.8
Adjusted, two-step Korn	–	17.6
Mean PFS[b]		
Unadjusted, modified Korn	20.6	8.0
Adjusted, modified Korn	–	15.2
Unadjusted, two-step Korn	18.2	7.4
Adjusted, two-step Korn	–	17.6

NR not reached, *OS* overall survival, *PFS* progression-free survival, *T-VEC* talimogene laherparepvec

[a] Data were pooled from the ipilimumab plus dacarbazine arm of the CA184-024, trial [27] that included only patients with previously untreated metastatic melanoma and also from the two ipilimumab arms (ipilimumab plus gp100, and ipilimumab monotherapy) of the MDX010-20 trial [21] that included only patients with previously treated metastatic melanoma

[b] Mean overall survival and progression-free survival calculated by area under the curve using the shorter available time period (55 months and 43 months respectively); prediction intervals were not presented by the company for PFS; time to treatment failure is used a proxy for progression-free survival for T-VEC

Source: adapted from Tables 42 to 46 of ERG report [17] (Crown copyright)

Box 1: Potential sources of bias highlighted in the OPTiM trial [18] highlighted by the ERG

- Durable response rate (DRR) is a subjective measure and is not a commonly used endpoint in other trials of metastatic melanoma
- Not all trial data were reviewed and confirmed by an independent, blinded Endpoint Assessment Committee (in the trial as a whole: 58% in the T-VEC arm, 87% in the GM-CSF arm)
- The definition of DRR allowed a patient to have a durable response (DR) even if the patient developed new lesions, relapsed, or progressed after the 6-month period when the DR was recorded;
- Perceived beliefs about the relative efficacy of T-VEC may also have influenced decisions about whether to stop treatment (particularly in the GM-CSF arm)
- In the trial as a whole, more patients withdrew their consent in the GM-CSF arm (8.5%) than in the T-VEC arm (3.4%)
- As noted by the US Food and Drug Administration [38], the proportion of patients who discontinued treatment at 3 months was 56.0% in the GM-CSF arm compared with 29.2% in the T-VEC arm.

ERG Evidence Review Group, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *T-VEC* talimogene laherparepvec