NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Talimogene laherparepvec for treating metastatic melanoma

This premeeting briefing presents:

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

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

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

Key issues for consideration

Clinical effectiveness

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

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

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

Cost effectiveness

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

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

- At 62 months in the company model there is a sudden unexplained increase in mortality, however the model assumes that all long-term survivors are effectively 'cured' at 10 years. Are these assumptions reasonable?
- The ERG commented that the derived ipilimumab survival trends were not reliable and are inadequate for estimating the cost effectiveness of T-VEC in people with non-visceral metastatic melanoma.
- The ERG's exploratory overall survival projections suggested that the company estimate for the mean overall of patients treated with T-VEC may be overstated by 49% to 59% leading to sizeable increases in the estimated ICERs.

1 Remit and decision problems

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

Table 1 Decision problem

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

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

2 The technology and the treatment pathway

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

Table 2 Technology

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

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

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

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

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

or

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

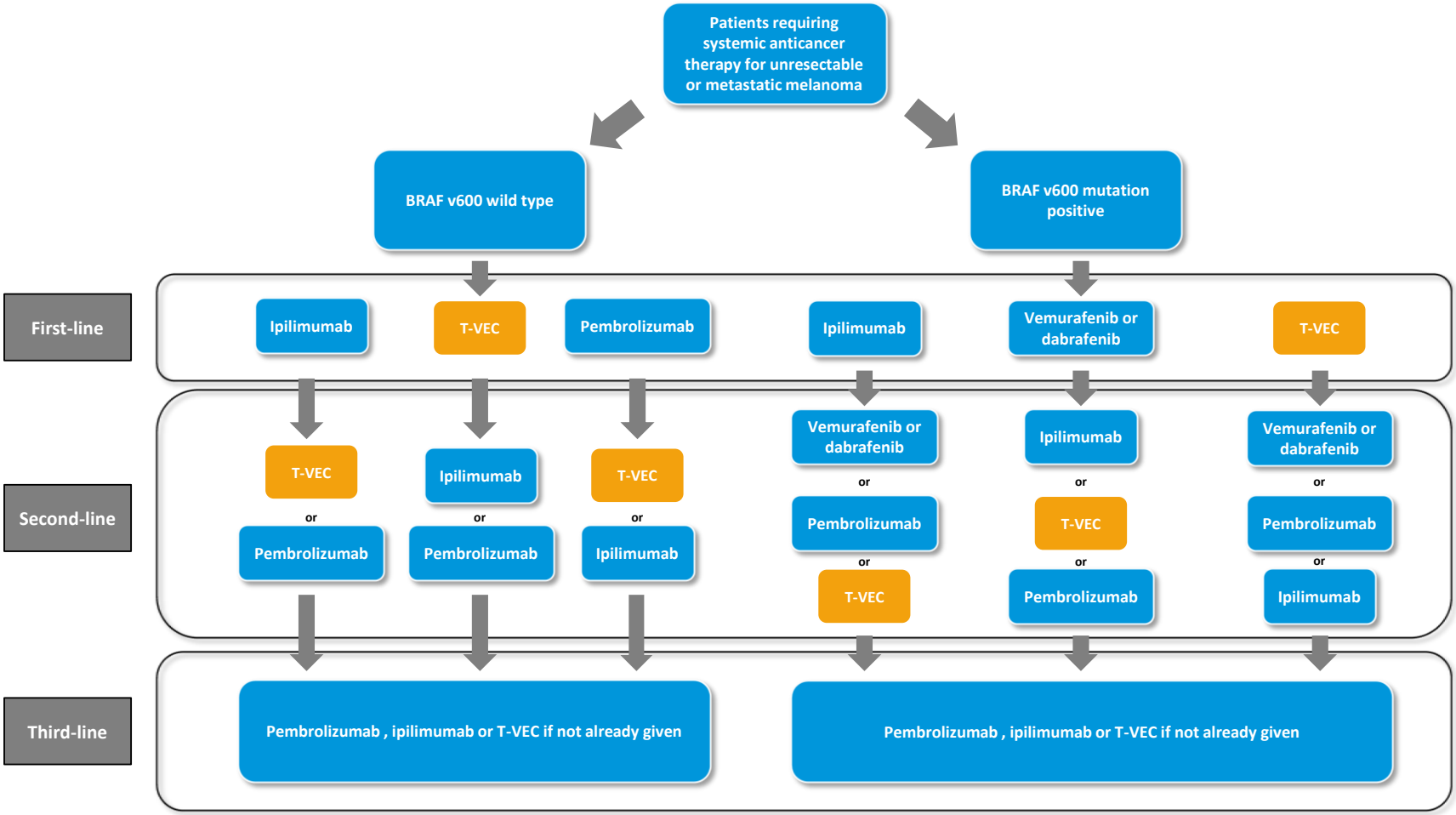
    any visceral organ and/or increased lactate dehydrogenase (LDH) levels in the serum, indicating aggressive tumour growth (stage IV M1c).

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

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

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

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



3 Comments from consultees

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

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

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

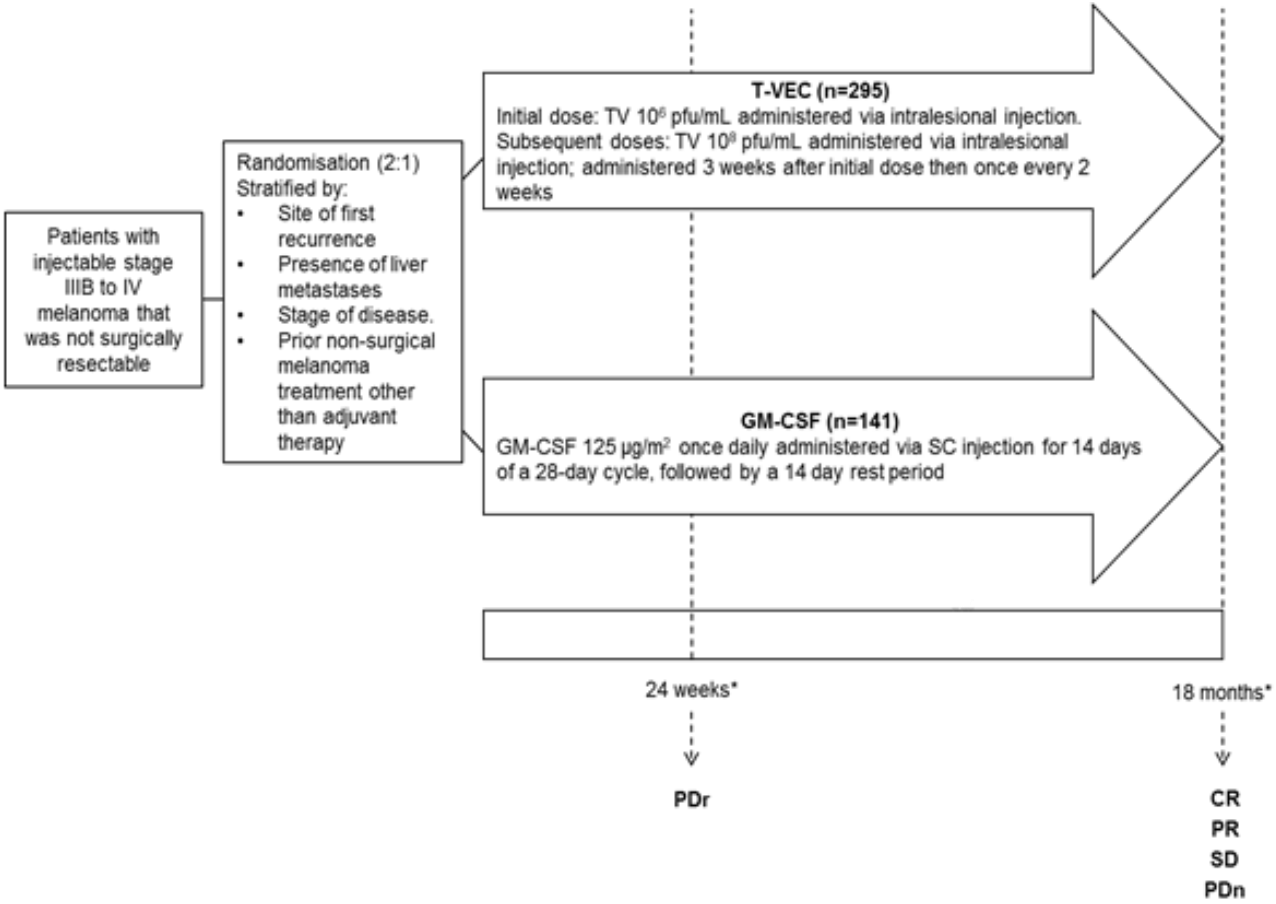
4 Clinical-effectiveness evidence

Overview of the clinical trials

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

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

Figure 2 OPTIM study design



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

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

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

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

ERG comments

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

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

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

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

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

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

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

Clinical trial results

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

Table 3 Clinical trial endpoints

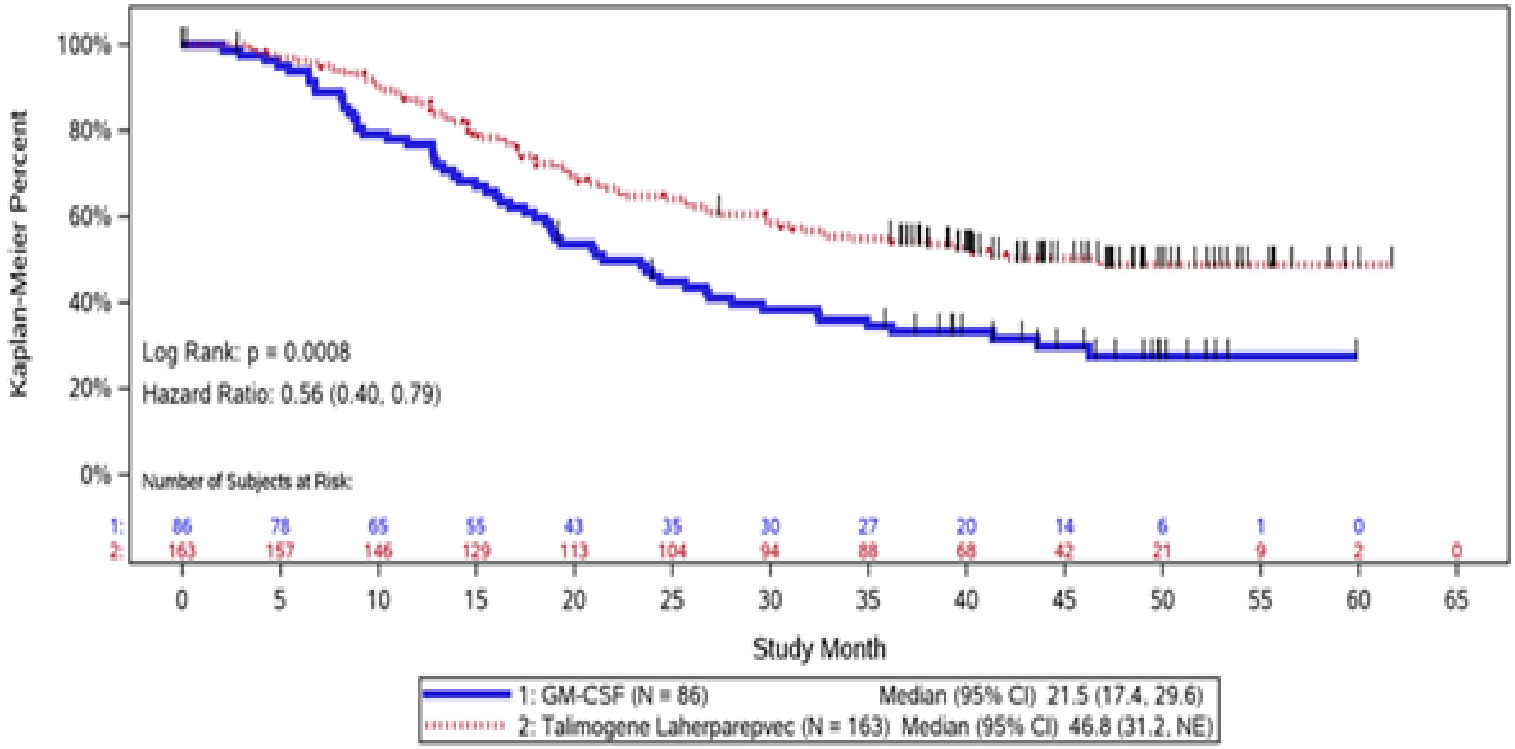
Endpoint	**OPTIM**	
	T-VEC (n=163)	**GM-CSF (n=86)**
Primary data cut – 31 March 2014		
Durable response rate	25.2%	1.2%
OR, p value	28.6, 0.0001	
Median overall survival (months)	41.1	21.5
HR, p value	0.57, 0.0009	
Median time to treatment failure (months) HR, p value	13.1	3.3
	0.27, 0.0001	
Overall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

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

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

4.12 Figure 3~~Figure 3~~).

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

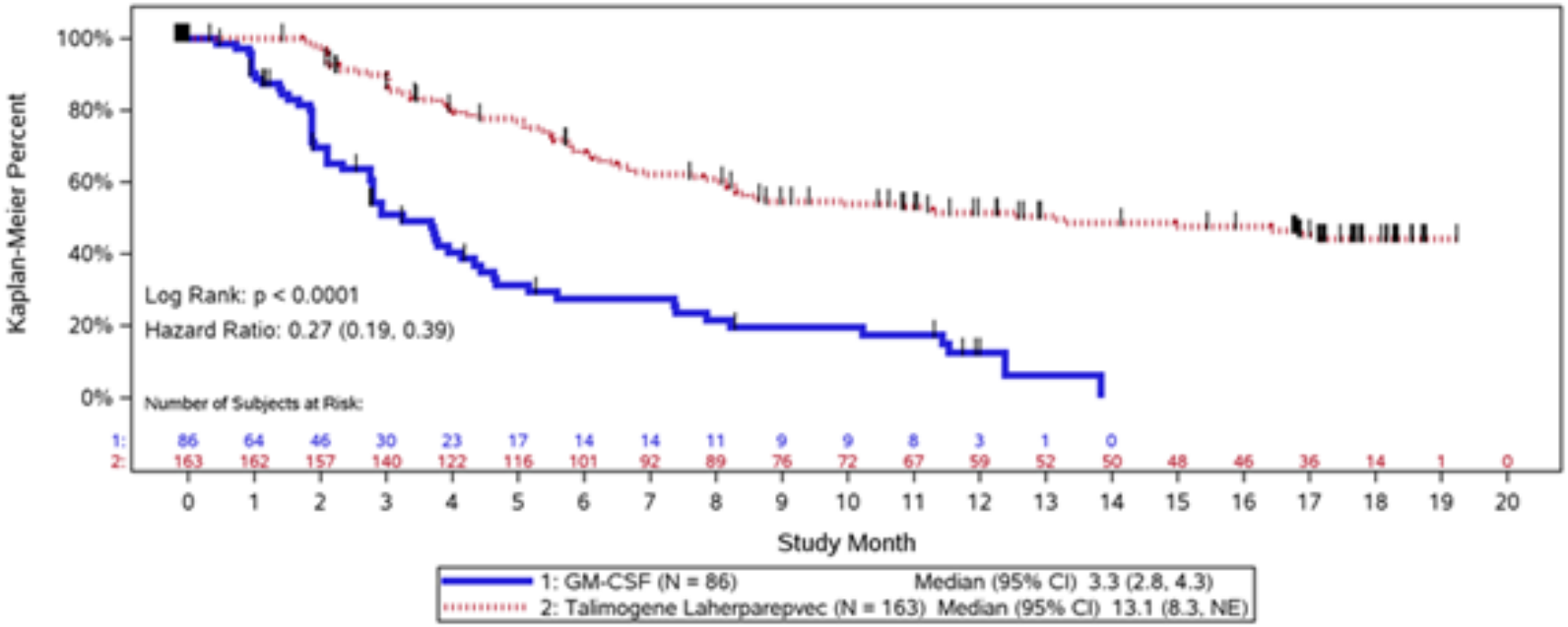


Source: company's submission, figure 4-6, page 69

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

4.13 Figure 4~~Figure 4~~).

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



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

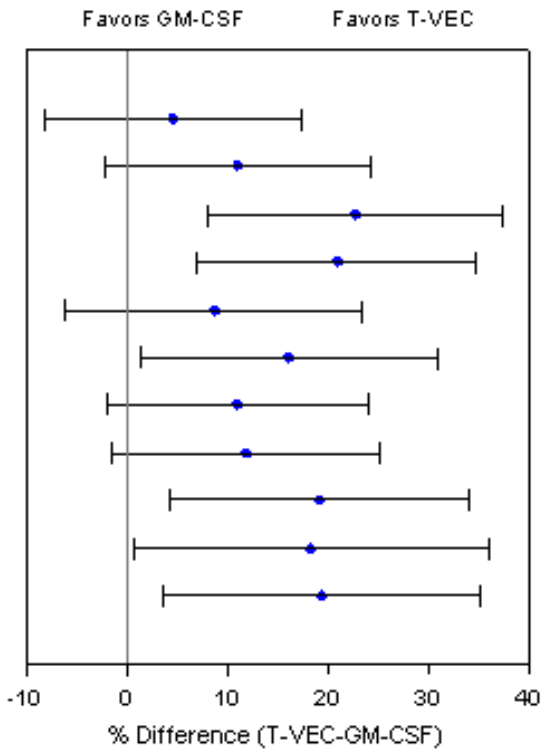
4.14 The company also presented results from exploratory analyses investigating the systemic activity of T-VEC, that is, beyond local effects in injected lesions. Results showed that in analyses of patients with non-injected lesions, 27 out of 79 patients (34.2%) had a more than 50% overall decrease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

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

4.15 Figure 5~~Figure 5~~).

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

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



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

ERG comments

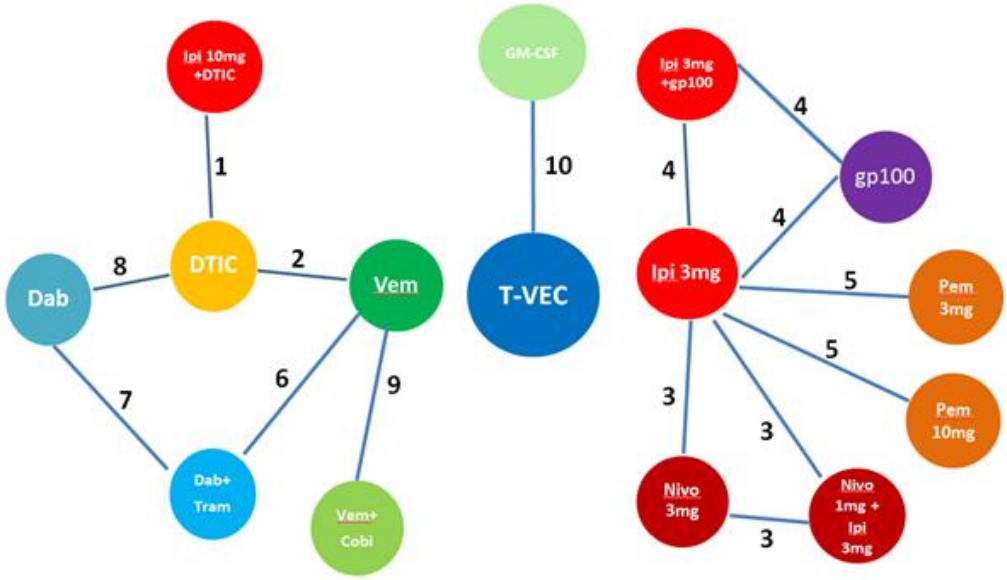
4.16 In the company submission, the results from people with non-visceral metastatic disease were consistent with the results from the ITT population. However, the ERG noted that the magnitude of difference between arms for all endpoints was much greater in patients with non-visceral metastatic disease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

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

Indirect comparison

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

Figure 6 Network diagram for indirect comparison



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

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

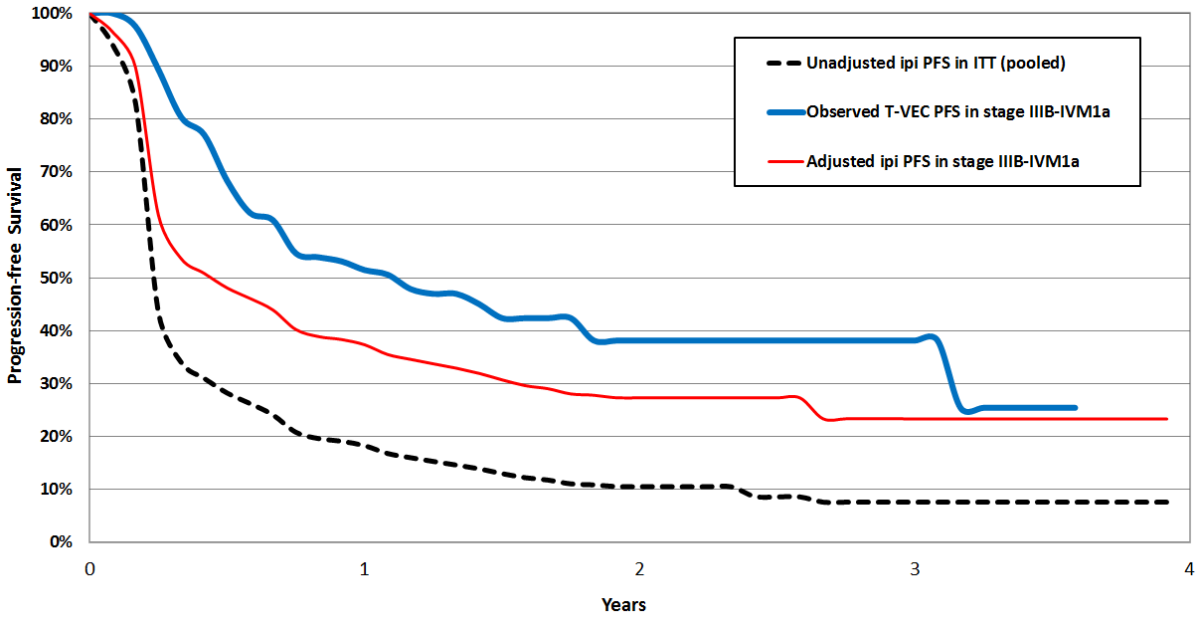
factor. The company stated that the modified Korn prediction model could also be used to adjust overall and progression-free survival data from each comparator. After assessing the feasibility of each method, the company concluded that given the differences in patient characteristics between trials,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

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

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

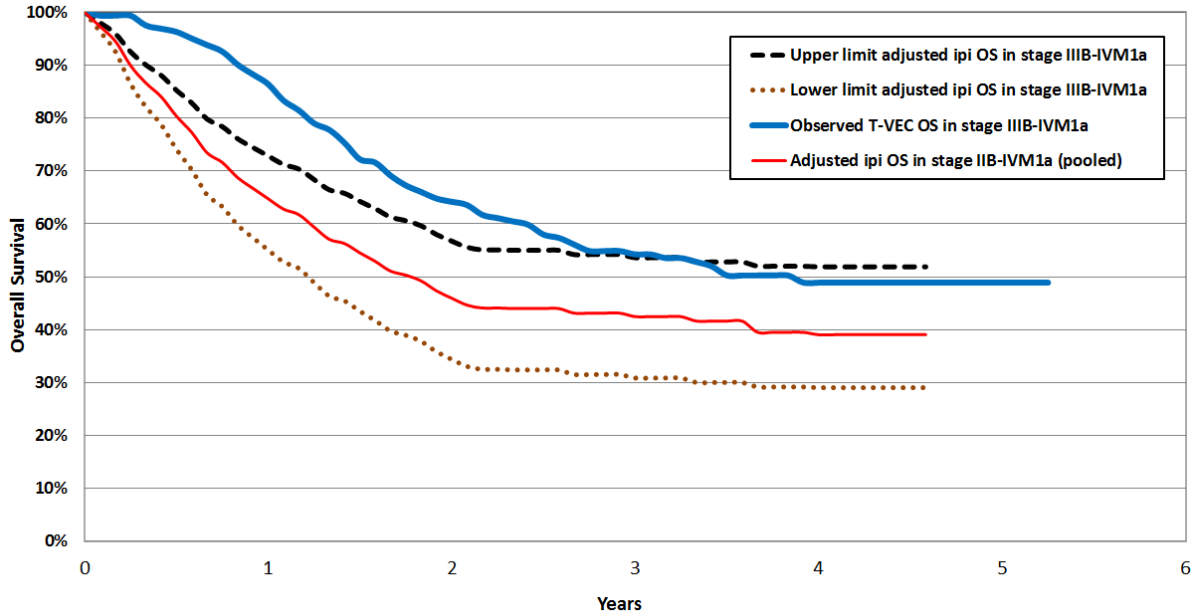
progression-free and overall survival. The company noted that these results were subject to considerable uncertainty because the modified Korn prediction model assumes that differences between studies in all measured and unmeasured confounders are captured by the prediction model and the adjustment factor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

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



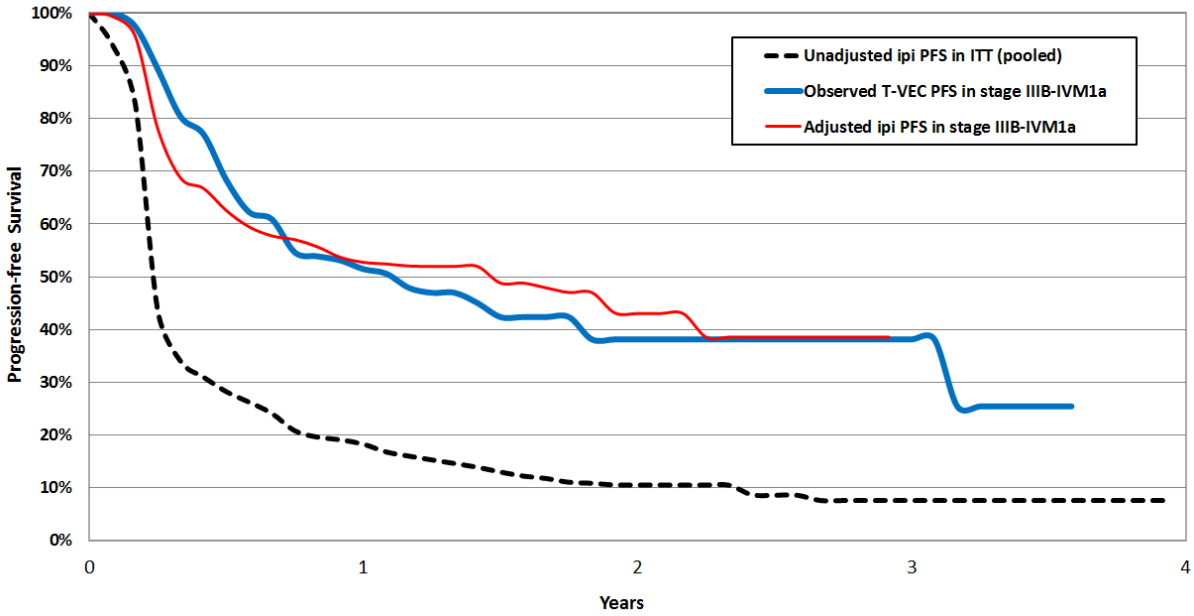
Source: company's submission, figure 4-13, page 92

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



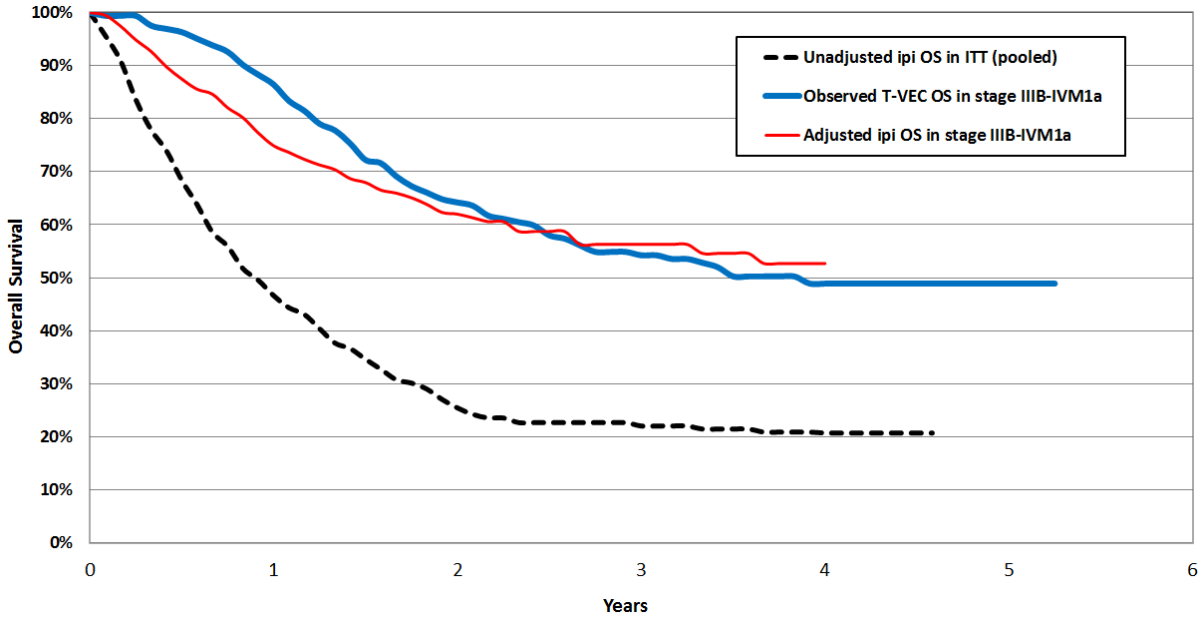
Source: company's submission, figure 4-14, page 92

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



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

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



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

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

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

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

ERG comments

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

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

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

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

Adverse effects of treatment

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

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

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

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

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

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

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

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

ERG comments

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

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

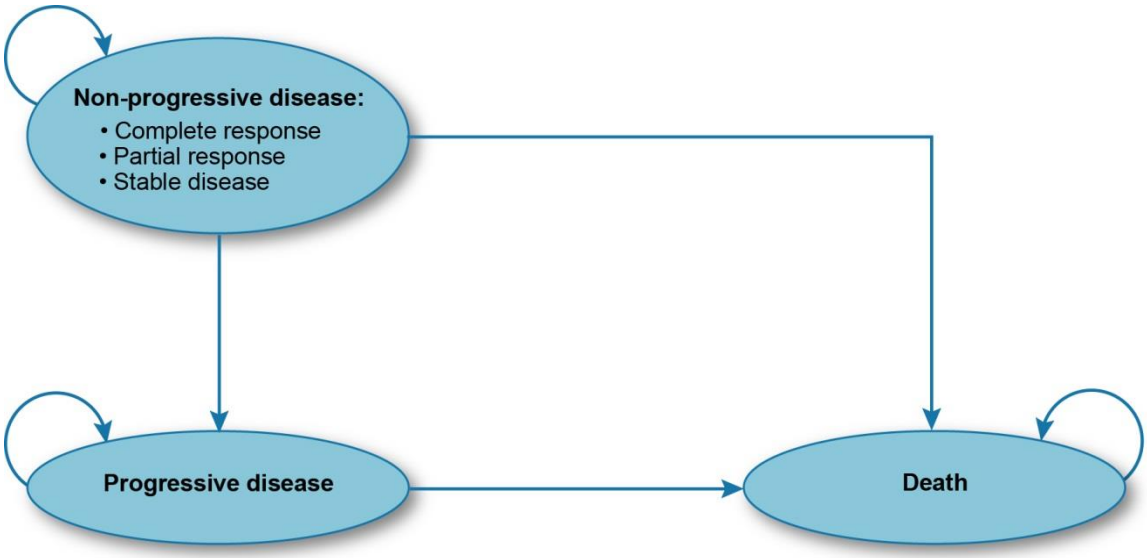
5 Cost-effectiveness evidence

Model structure

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

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

Figure 11 Company's model structure



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

ERG comments

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

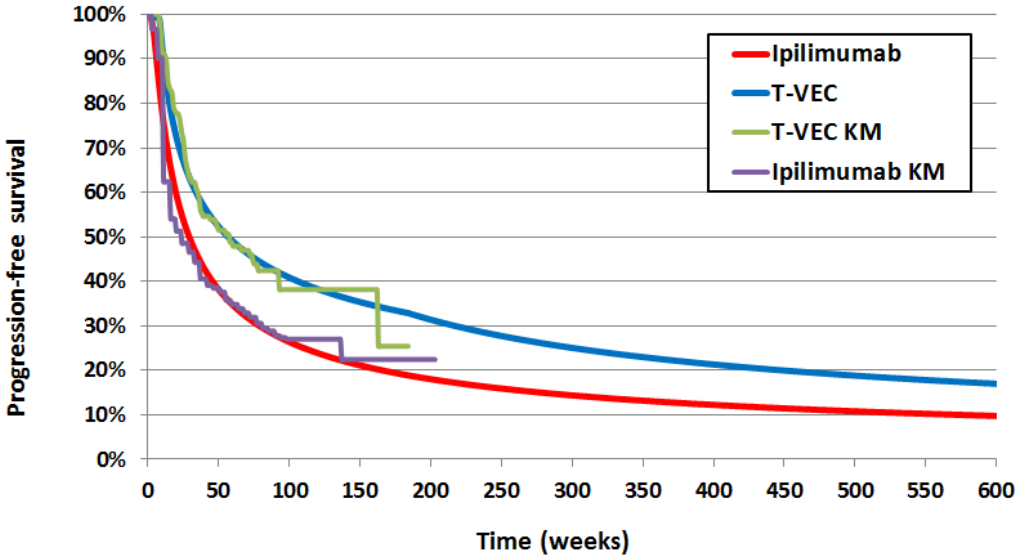
Model details

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

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

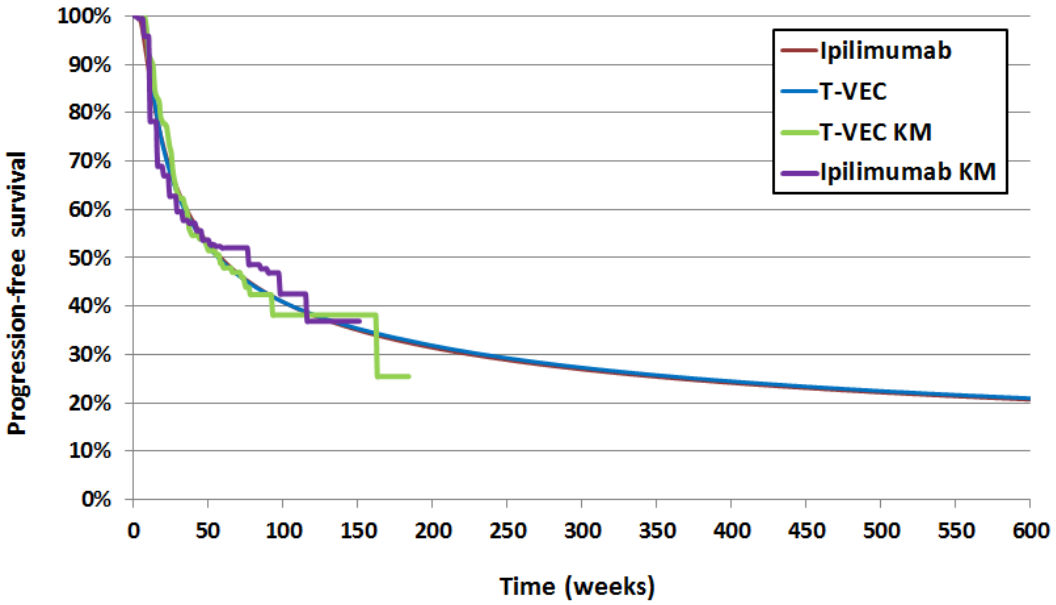
generalised gamma distribution provided the best fit to the data for T-VEC and ipilimumab. Figure 12 and Figure 13 show the progression-free survival estimates used in the model based on the modified Korn prediction model and the 2-stage Korn adjustment respectively. The company stated that because of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

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



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

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



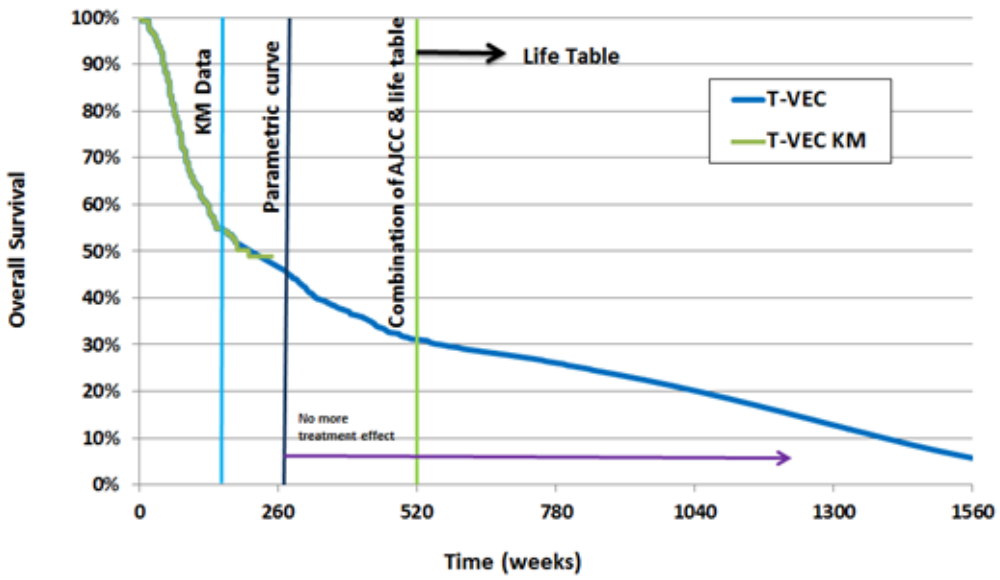
Source: company's submission, figure 5-27, page 146

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

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

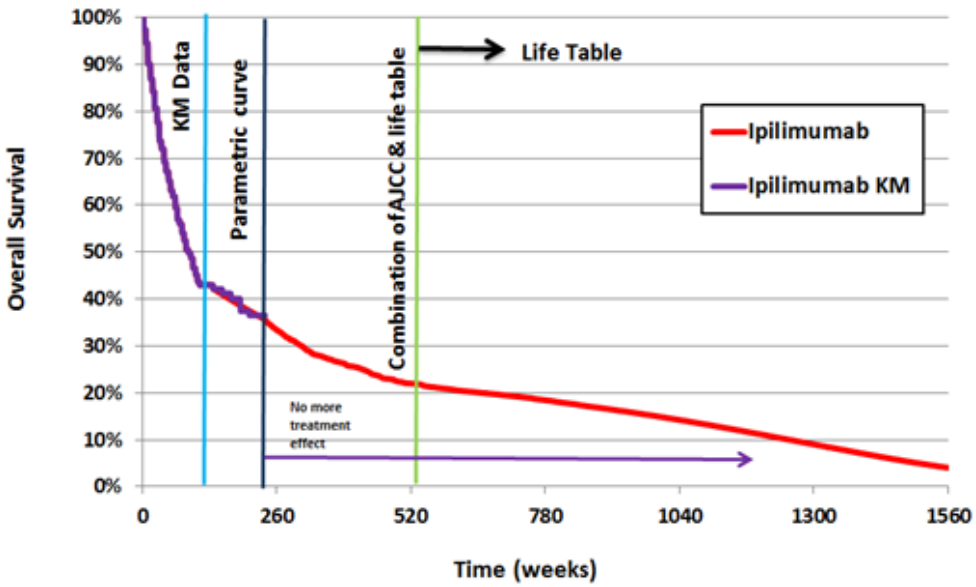
Figure 14 – Figure 16 show the results of the 3-part curve fit for overall survival used in the model

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



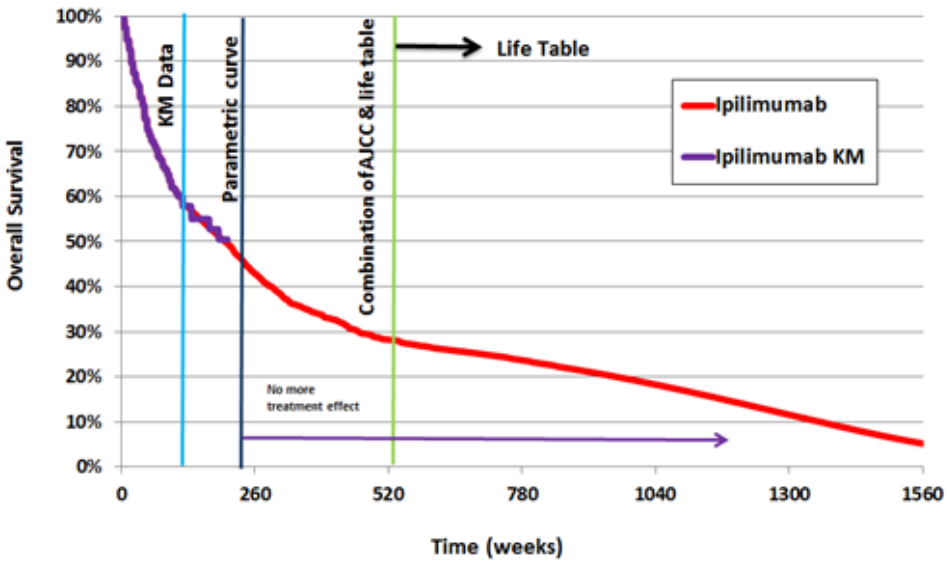
Source: company's submission, figure 5-13, page 137

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



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

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



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

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

Table 5 Table Adverse events included in the model

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

Table 6 Summary of utility values in the model

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

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

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

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

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

ERG comments

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

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

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

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

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

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

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

Company's base-case results and sensitivity analysis

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

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

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

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

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

ERG comments

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

Company scenarios

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

ERG exploratory analyses

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

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

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

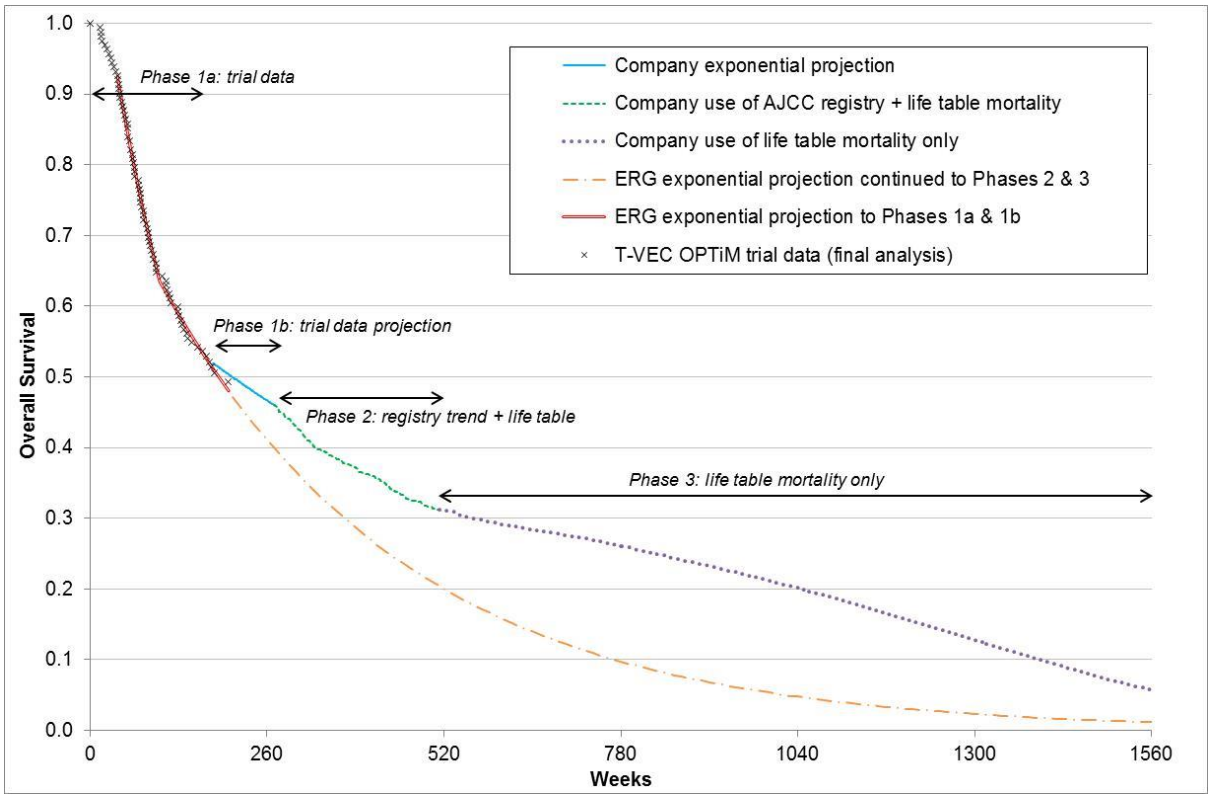


Figure 16. Company long-term T-VEC overall survival projection compared to ERG simple exponential alternative projection (see figure 8, page 89 of the ERG report).

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

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

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

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

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

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

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

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

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

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

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

- All of the other issues identified when considered individually had a very small impact on the position of T-VEC, generally increasing the size of the estimated ICER per QALY gained.
- When the PAS for ipilimumab was applied alongside the ERG's overall survival and progression-free survival estimates, the ICER per QALY gained was increased to a value far beyond the range normally considered acceptable.
- The cost effectiveness of T-VEC compared to ipilimumab varies from dominating (more effective at less cost in the modified Korn model) to being dominated (less effective at greater cost in the two-step Korn model).

Innovation

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

- It is a first-in-class oncolytic immunotherapy with a dual mechanism of action that produces local tumour control and systemic anti-tumour immune responses
- It is administered by intralesional injection
- It is the only treatment approved specifically in patients with regionally or distantly metastatic melanoma with no visceral disease (stage IIIB-IVM1a disease) and has shown a major clinical advancement in treatment for this population
- It is associated with fewer treatment-related grade 3 and 4 adverse events compared with other existing treatment options for advanced melanoma.

6 Equality issues

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

7 Authors

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

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