

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Talimogene laherparepvec for treating unresectable metastatic melanoma [ID508]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
 - Amgen
 - Melanoma Focus and Royal College of Physicians
 - British Association of Dermatologist – *provided no comment*
 - Department of Health – *provided no comment*
 - Royal College of Nursing –*provided no comment* Consultee and commentator organisations
3. **Comments on the Appraisal Consultation Document from experts:**
 - Clinical expert, nominated by Royal College of Physicians.
 - Clinical expert, nominated by Amgen
4. **Comments on the Appraisal Consultation Document received through the NICE website**
5. **ERG addendum post ACD**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Talimogene laherparepvec for treating unresectable metastatic melanoma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Amgen	<p>Suitability of the Korn methods to adjust ipilimumab survival data to earlier stage disease .</p> <ul style="list-style-type: none"> • The Korn methods are suitable to adjust ipilimumab survival data to earlier stage, non-visceral (IIIB, IIIC and IVM1a) disease: The development of the original Korn model included patients with stage IVM1a disease and there is robust evidence to show that the disease trajectories for unresectable, stage IVM1a and stage IIIB/C are similar. • It is not correct to suggest that the inclusion of an adjustment for lactate dehydrogenase (LDH) level in the modified Korn method leads to an overestimate of the efficacy of talimogene laherparepvec. Instead it was a conservative approach which increased the estimate of OS for ipilimumab. • Given the significant logical and clinical inconsistencies associated with the original Korn PFS model, we do not consider it appropriate for use and consider the use of the same modified Korn model for both OS and PFS to be more suitable. • The Korn models are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show talimogene laherparepvec is at least as effective as ipilimumab in the worst-case scenario 	<p>Comment noted. The committee considered the arguments to support the use of the Korn methodology in the population of the marketing authorisation (IIIB, IIIC and IVM1a).</p> <p>The committee considered the Korn method to be flawed for modelling progression in stage IIIB–IVM1a disease because the algorithm was developed using data from people with predominantly stage IVM1B and stage IVM1c disease, which have different disease trajectories see FAD section 4.9).</p>

Consultee	Comment [sic]	Response
Amgen	<p>Analyses using Korn methods to compare talimogene laherparepvec with ipilimumab in the broader population of patients including later stage disease</p> <ul style="list-style-type: none"> • Korn methods have been used within previous appraisals and accepted by NICE as a suitable method for evaluation of comparative efficacy in a broader population of patients with stage IIIB-IVM1c disease. • Therefore evaluation in the broader OPTiM ITT (stage IIIB-IVM1c) population which includes a substantial proportion of later stage patients, removes the criticisms raised by the Committee regarding suitability of the Korn methods. • Analyses conducted in this broader population also showed that talimogene laherparepvec is at least as effective as ipilimumab. • This adds to the level of certainty that talimogene laherparepvec would also be at least as effective as ipilimumab in earlier stage disease, given that talimogene laherparepvec efficacy is greater in this population. 	<p>Comment noted. The committee considered the arguments to support the use of the Korn methodology in the population of the marketing authorisation (IIIB-IVM1c).</p> <p>The committee noted that these analyses did not address the underlying methodological concern that the Korn algorithm (which was based predominantly on patients with later stage disease) was not valid because it had not been calibrated against patient level data from ipilimumab trials in a similar population to the OPTIM trial (see FAD section 4.9 and 4.13).</p>
Amgen	<p>Analysis using conventional ITC methods to compare talimogene laherparepvec with ipilimumab in earlier stage disease</p> <ul style="list-style-type: none"> • We present an analysis showing that GM-CSF is at least as clinically effective as DTIC and gp100 regardless of disease stage. • Assuming (conservatively) equivalence of GM-CSF with DTIC and gp100 then allowed a simple ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease. • The results of the ITC showed a trend towards a more favourable survival effect for talimogene laherparepvec although there was no statistically significant difference in OS for talimogene laherparepvec compared with ipilimumab in earlier stage disease: HR (95% CI) 0.87 (0.53, 1.45) (P=0.61). • Analysis using ITC methods to compare talimogene laherparepvec with ipilimumab in earlier stage disease shows that talimogene laherparepvec is at least as effective as ipilimumab. The ITC provides an alternative approach to that of Korn, thereby providing external validity to the previous findings. 	<p>Comment noted. The committee noted that the company's naïve indirect comparison of talimogene laherparepvec with ipilimumab (in which GM-CSF, dacarbazine and gp100 were assumed to be equally ineffective in the treatment of metastatic melanoma) but did not consider it to be a reliable method of establishing the relative effectiveness of these agents (see FAD section 4.14).</p>

Consultee	Comment [sic]	Response
Amgen	<p>Cost effectiveness of talimogene laherparepvec versus ipilimumab</p> <ul style="list-style-type: none"> • We believe the Committee is incorrect to state that OS with talimogene laherparepvec could be less favourable than with ipilimumab using the ERG method. • The ERG approach to OS extrapolation does not represent the trajectory of metastatic melanoma patients and is not clinically plausible. In contrast the Amgen extrapolation more closely matches observed 10 year survival data in melanoma patients and also aligns with the approach for the previous NICE appraisals for ipilimumab. • This ERG approach is not an appropriate basis on which to inform judgements about the OS of talimogene laherparepvec as it appears to have only considered data up to the last recorded death and ignored the full survival times of patients, thereby incorrectly stating that the company model exponential trend deviated markedly from the final recorded trial data. • Furthermore, the ERG applied its extrapolation approach only to talimogene laherparepvec rather than consistently applying its method to both treatments and, as a result, misleadingly concluded that talimogene laherparepvec OS could be worse than ipilimumab. • We demonstrate that as long as the same approach is applied to both therapies (as opposed to only talimogene laherparepvec), the difference in OS is at least comparable and that talimogene laherparepvec still remains cost effective versus ipilimumab. • Additionally, company assumptions made for the OS extrapolation beyond trial follow-up were consistently conservative, and further support the claim that talimogene laherparepvec is cost effective versus ipilimumab. 	<p>Comment noted. The committee could not be confident that talimogene laherparepvec had been convincingly shown to be at least as effective as ipilimumab in this patient group (see FAD section 4.9).</p> <p>The committee concluded that, because of the lack of suitable effectiveness inputs in the economic model, it had not been presented with a plausible incremental cost effectiveness ratio (see FAD section 4.12).</p>

Consultee	Comment [sic]	Response
Amgen	<p>Cost effectiveness of talimogene laherparepvec versus recognised treatments (DTIC) and BSC</p> <ul style="list-style-type: none"> • We have demonstrated that GM-CSF is at least as clinically effective as recognised treatments (DTIC) and BSC (gp100) and therefore the OPTiM GM-CSF arm can be used conservatively as a proxy for DTIC and BSC, allowing evaluation of cost effectiveness of talimogene laherparepvec versus these treatments • Talimogene laherparepvec is highly cost effective versus recognised treatments (DTIC) and BSC with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that talimogene laherparepvec is cost effective versus ipilimumab. • This analysis benchmarks the cost effectiveness of talimogene laherparepvec versus the approach taken for ipilimumab, removing the uncertainty associated with the lack of evidence for ipilimumab in the earlier stage disease population, and adds further certainty to the assessment of the cost effectiveness of talimogene laherparepvec 	<p>Comment noted. The committee considered whether there may be a subgroup of patients for whom talimogene laherparepvec would be particularly beneficial. It considered the additional analyses on the cost effectiveness of talimogene laherparepvec compared with dacarbazine (which has not been shown to prolong overall survival), and best supportive care. These analyses were an indication of the cost effectiveness of talimogene laherparepvec in people for whom existing systemically administered immunotherapies would not be appropriate. The committee concluded that talimogene laherparepvec is a clinically and cost-effective option for people with unresectable non-visceral metastatic melanoma for whom systemically administered immunotherapies are unsuitable (see FAD section 4.16).</p>

Consultee	Comment [sic]	Response
Amgen	<p>Post-hoc nature of the licensed subgroup forming the clinical evidence base for talimogene laherparepvec</p> <p>Although the specific combination of stage IIIB to IVM1a disease was not pre-specified as a subgroup in OPTiM, subgroup analysis by disease stage was pre-specified (IIIB/C, IVM1a, IVM1b, IVM1c), as acknowledged in Table 7 of the ERG report (NICE ID508, 2016). This pre-specified analysis showed that efficacy was most pronounced in stage IIIB/C and IVM1a disease which led to the licensed indication in earlier stage disease.</p> <p>The credibility of the disease stage subgroup analyses was fully discussed with the EMA and the EPAR acknowledges that these analyses adhered to the EMA guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013), stating that “robust statistical analyses based on pre-specification of covariate, replication across studies (study 005/05 and 002/03), consistency across endpoints, statistical significance of treatment-by-covariate interaction and biological plausibility of the observed effect” were performed (EMA, 2015).</p> <p>The main concern raised around the post-hoc nature of the licensed subgroup is that it includes patients with stage IIIB/C disease and patients with stage IVM1a disease who are likely to have different disease trajectories. However, data presented in section 1.1 show that the disease trajectory is similar in those with stage IIIB/C and IVM1a disease (Song et al, 2015).</p> <p>In summary, although the specific grouping of stage IIIB-IVM1a disease was not pre-specified as a subgroup in OPTiM, analysis by disease stage was pre-specified and adhered to regulatory guidance, and resulted in the approved EMA indication.</p>	<p>Comment noted. The committee assessed the evidence for the clinical and cost effectiveness of talimogene laherparepvec based on the population in the marketing authorisation.</p>

Consultee	Comment [sic]	Response
<p>Melanoma Focus and RCP (also endorsed by n NCRI-RCP-ACP)</p>	<p>The Appraisal Consultation Document accurately summarises the advances made in the treatment of metastatic melanoma in the last five years. The UK is in the privileged position of having many of these treatments available for patients. However, despite a significant improvement in the median survival for patients, from 9 months to approximately 30 months, the majority of patients with advanced disease still die of melanoma. Additionally, there are groups of patients with a high risk of toxicity from existing strategies (ipilimumab or pembrolizumab) because of pre-existing autoimmune conditions, for whom ipilimumab and pembrolizumab are not suitable. Further treatment options and newer treatment strategies are urgently required.</p> <p>Oncolytic therapy such as talimogene laherparepvec (T-VEC) is one such approach for patients with locally advanced (inoperable stage 3), or stage 4 M1a disease. The ACD correctly summarised the outcome of the OPTIM study, noting the challenges provided by the use of a non-standard trial endpoint and study comparator. Nevertheless, the OPTIM study identified a subgroup of patients with durable responses and this led to the approval of T-VEC by the FDA and EMA.</p> <p>T-VEC is a first-in-class agent with a novel dual action. A major advantage is the low risk of significant toxicity and the potential for systemic benefit from a local therapy, in contrast to existing immune therapies. Approximately 10%-15% of patients have troublesome locally advanced or 3c/M1a disease. Whilst these patients are likely to benefit from the current NICE-approved agents, they are also the group of patients who will benefit from T-VEC. Increasing treatment options for patients (ie targeted therapy and immunotherapy) have already been shown to improve survival in advanced melanoma, so it is logical to further expand new treatment options for eligible patients.</p>	<p>Comment noted.</p> <p>The committee noted that additional options for the treatment of advanced melanoma are beneficial to patients and carers (see FAD section 4.3).</p> <p>The committee considered the clinical and cost effectiveness of talimogene laherparepvec and recommended it's use in people for whom treatment with systemically administered immunotherapies are unsuitable (see FAD section 4.16).</p>

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
NCRI/RCP/RCR/ACP	<p>The Appraisal Consultation Document accurately summarizes the advances made in the treatment of metastatic melanoma in the last five years. The UK is in the privileged position of having many of these treatments available for patients. However, despite a significant improvement in the median survival for patients, from 9 months to approximately 30 months, the majority of patients with advanced disease still die of melanoma. Additionally, there are groups of patients with high risk of toxicity from existing strategies (ipilimumab or pembrolizumab) because of pre-existing autoimmune conditions or previous toxicity, for whom ipilimumab and pembrolizumab are not suitable. Further treatment options and newer treatment strategies are urgently required.</p> <p>Oncolytic therapy such as talimogene laherparepvec (TVEC) is one such approach for patients with locally advanced (inoperable stage 3), or stage 4 M1a disease. The ACD correctly summarised the outcome of the OPTIM study, noting the challenges provided by the use of a non-standard trial endpoint and study comparator. Nevertheless, the OPTIM study identified a subgroup of patients with durable responses , and this led to the approval of TVEC by the FDA and EMA.</p> <p>TVEC is a first-in-class agent with a novel dual action. A major advantage is the low risk of significant toxicity and the potential for systemic benefit from a local therapy, in contrast to existing immune therapies.</p> <p>Approximately 10-15% of patients have troublesome locally advanced or 3c/M1a disease. Whilst these patients are likely to benefit from the current NICE-approved agents, they are also the group of patients who will benefit from TVEC. Increasing treatment options for patients (ie targeted therapy and immunotherapy) have already been shown to improve survival in advanced melanoma, so it is logical to further expand new treatment options for eligible patients.</p>	<p>Comment noted.</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable</p>

Nominating organisation	Comment [sic]	Response
<p>NCRI/RCP/RCR/ACP (continued)</p>	<p>A major challenge for the NICE Appraisal of TVEC was the lack of a standard comparator; the comparator used in the OpTIM trial is clinically inactive, ie was a placebo. Although Ipilimumab was approved as a standard comparator, in retrospect either an anti-P1 antibody, targeted therapy or electrochemotherapy would have been more appropriate. Compared to ipilimumab, TVEC stands up well in terms of efficacy, durable benefit and, importantly, very low risk of toxicity. For many eligible patients, TVEC would be given in preference to other licensed and approved treatments.</p> <p>Review in our own clinical practice (Southampton) since the previous committee meeting has identified three patients presenting in the intervening weeks, who would be excellent candidates for T-VEC treatment as they fit the EMEA treatment criteria but were not suitable for immunotherapy due to previous toxicity or pre-existing autoimmune disease. These patients will lose out if they cannot be offered T-VEC.</p> <p>The next major advance in the treatment of melanoma will be combination immunotherapy. Early studies combining TVEC with ipilimumab, and TVEC with anti-PD1 antibodies, have shown significant activity in converting non-responding patients to become responders. This has a huge implication not just for melanoma but for many other cancers including sarcoma, head-and-neck cancer and breast cancer. Whilst not directly pertinent to the NICE decision, there is risk that if patients cannot access TVEC within the licensed indication, this may impact on future developments in combination.</p> <p>In summary, TVEC is an appropriate treatment for a small subgroup of patients. It is an effective treatment with substantially less risk of significant toxicity compared to ipilimumab, and with advantages over the other potential treatment options not considered in the NICE Appraisal. Talimogene laherparepvec would be the treatment of choice for a limited number of patients.</p>	

Nominating organisation	Comment [sic]	Response
Amgen	<p>I am writing to express my grave disappointment at the recent result issued by the NICE Appraisal Committee that heard evidence on T-VEC. If this result is ratified, it will result in this novel technology being unavailable to patients in the NHS. I believe that there are grounds to ask the committee to reconsider its position.</p> <p>It appears that the main reason for ruling against T-VEC was based on an unwillingness to accept the indirect comparison of T-VEC with Ipilimumab (despite the fact that this was the remit under which the evaluation was conducted). This matter relates largely to the fact that there is no directly comparable dataset to provide data on the activity of Ipilimumab in the population that is the target group for T-VEC. This judgement was made despite efforts to provide a modelled dataset based on Korn (and modified Korn) methodology. I believe that there are grounds to re-visit this issue and to contest the assertion of the reviewers that there is a risk that T-VEC may, in fact, be significantly inferior to T-VEC. Having said that, in the absence of a head-to-head trial of T-VEC vs Ipi (or another immunotherapy) modelled data such as those that were presented represent the only possible way of setting a new technology like T-VEC in context in a population of melanoma patients with stage IIIB/IIIC/IVM1a disease. If modelled data are not used as a basis of comparison, I am very concerned that there is no way in which to assess T-VEC fairly and to give patients the prospect of receiving this therapy. As a specialist who treats patients with melanoma – including patients who meet the European indications for its use – I am alarmed that this treatment may be denied to patients who, in my opinion, stand a very high chance of deriving clinical benefit.</p> <p>The importance of treatment-related toxicities has been discussed but, in my opinion, the very low toxicity burden of T-VEC may not have been given appropriate consideration. T-VEC is markedly different from existing, licensed immunotherapies and may represent a very favourable treatment option for specific patient groups. Again, I hope that matter is considered once more.</p> <p>The committee noted the novelty of the therapy – but this did not sway the overall decision. Again, I believe that there are grounds to revisit this matter and to consider T-VEC as a unique technology that has the potential to change the way in which melanoma is treated.</p> <p>Overall, I would hope that there is an opportunity to appeal this initial ruling and to have a chance to make this treatment available for patients who stand to derive very significant benefits.</p>	<p>Comment noted.</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable</p>

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Comments received from commentators - None

Comments received from members of the public through the NICE web site

Role*	Comment [sic]	Response
<p>NHS Professional 1</p>	<p>I am a medical oncologist working at Guy's and St Thomas NHS Foundation Trust treating malignant melanoma. I am the lead for skin cancer research in the Trust and a clinical academic involved in solid tumour T-cell immunotherapy research. I am the local principle investigator on a phase 2 study of talimogene laherparevec in melanoma. We have treated the largest group of patients on this trial to date.</p> <p>Having read the appraisal consultation document it is clear that there is difficulty in deciding on the first in class advanced therapy medicinal product (ATMP) talimogene laherparepvec's efficacy based on the patient population covered by the license. The majority of patients treated with the NICE scope comparator Ipilimumab with unresectable stage IIIB-IVM1a was low. In practice these patients are managed depending on the distribution of their disease. Modalities such as ECT and isolated limb perfusion (for which reliable randomised data supporting efficacy does not exist) are used but, in this new era of systemic immunotherapy, we are moving to treat with checkpoint inhibition. So, in clinical practice, the majority of patient with unresectable stage IIIB-IVM1a melanoma will receive CTLA4 or PD1 directed immunotherapy. These agents come with the risk of systemic autoimmune toxicities which can, on occasion, be severe for patients. In this patient population, where therapy is needed and evidence is thin on the ground, data from the 57% of patients on the OPTiM trial with stage IIIB-IVM1a disease offers solid randomised evidence that there is now an effective therapy. In my view the lack of a clear cross comparator from other systemic therapy trials only serves to highlight the importance of this exciting ATMP for a group of patients who have long been in need of effective therapy.</p> <p>Our experience with talimogene laherparepvec is, for well selected patients with accessible and injectable disease, the drug represents an excellent, innovative and very well tolerated alternative to both therapies such as ECT and limb perfusion and systemic immunotherapy. The treatment causes minimal and manageable side effects and can be given in clinic avoiding the need for chair space on our busy cancer day unit.</p>	<p>Comment noted. The committee were aware that the OPTiM trial represents the best evidence for this stage of disease (see FAD section 4.7).</p> <p>However, although the company had made efforts to make a comparison with ipilimumab there was considerable uncertainty of that comparison, largely because of the lack of efficacy data for ipilimumab in the relevant population (see FAD section 4.8).</p> <p>The committee considered that the company should be complimented on their thorough approach to the problem of defining an appropriate comparison with ipilimumab from the available trial data. However, it accepted the underlying concern of the ERG that the Korn method was flawed for modelling progression in stage IIIB–IVM1a disease because the algorithm was developed using data from people with predominantly stage IVM1B and stage IVM1c disease, which have different disease trajectories. However, on the evidence available, the committee could not be confident that talimogene laherparepvec had been convincingly shown to be at least as effective as ipilimumab in this patient group (see FAD section 4.9).</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable</p>

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role	Comment [sic]	Response
<p>NHS Professional 1 (continued)</p>	<p>Our experience with talimogene laherparepvec is, for well selected patients with accessible and injectable disease, the drug represents an excellent, innovative and very well tolerated alternative to both therapies such as ECT and limb perfusion and systemic immunotherapy. The treatment causes minimal and manageable side effects and can be given in clinic avoiding the need for chair space on our busy cancer day unit.</p> <p>Treating unresectable melanoma is a rapidly evolving field. The paradigm shift from cytotoxic agents to targeted therapy and immunotherapy over the past 5 years has dramatically changed the landscape of survival for patients. Having talimogene laherparepvec as one of the options for patients in the NHS is key to ensuring we are offering the best possible therapy for our patients - allowing innovation to impact on outcomes.</p>	
<p>NHS Professional 2</p>	<p>I am a clinician scientist specializing clinically in melanoma, and in translational immunotherapy in my research. I have recently moved to the Institute of Cancer Research in London, and my specific interest is in oncolytic immunovirotherapy. I have published extensively in this field, across the research spectrum, from pre-clinical studies to early clinical trials (including biological endpoint translational studies). My opinion is that TVEC is an Advanced Therapeutic Medicinal Product, and represents genuine innovation in the treatment of melanoma. In my experience having taken part in TVEC trials and administered the virus to patients, TVEC is in general well tolerated compared to many existing therapies (eg ipilimumab), and acceptable to patients, and would be a useful treatment option for the small number of patients with injectable stage IIIB/C/IVM1a disease.</p> <p>TVEC, if it behaves as do other immunotherapies (which is what I would expect as the data matures), offers the hope, even as a single agent, for inducing prolonged periods of remission in this small group of appropriate patients.</p> <p>Importantly other treatments which may currently be prescribed for patients with Stage IIIB/C/IVM1a disease (including BRAF inhibitors as well as checkpoint inhibitor antibodies), all have the potential for associated significant, and sometimes severe, side effects which may make their use less desirable in patients with low volume, slowly progressing metastatic disease, for whom TVEC would be an alternative, earlier treatment.</p>	<p>Comment noted. The committee agreed that intra-lesion injections are an innovative approach to the treatment of melanoma, although the marketing authorisation did not support the systemic action of talimogene laherparepvec. However, the committee could not identify any specific health related benefit that had not already been captured in the QALY calculation (see FAD section 4.17).</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable.</p>

Role	Comment [sic]	Response
<p>NHS Professional 2 (continued)</p>	<p>It is worth noting that TVEC is effective in treating melanoma regardless of BRAF status. For patients with relatively low volume, good prognosis metastatic disease it is becoming increasingly attractive to treat BRAF mutant patients with an immunotherapy first, reserving BRAF inhibitors for later therapy; indeed, this is an approach increasingly being requested by patients themselves in the clinic. This is understandable and appropriate, given the increasing evidence that immunotherapies offer the potential for sustained benefit, as illustrated by the long-term survival figures of around 20% in patients given CTLA4 blockade.</p> <p>Although BRAF inhibitors have a higher response rate than immunotherapies, no such long-term “tail” on the survival curve is seen. It is my opinion that the same long-term remissions are likely to be seen in due course in a proportion of patients treated with intratumoural T-Vec, regardless of BRAF status (even beyond the 5 years follow up we currently have data for)</p> <p>The treatment scheduling of treatment in metastatic melanoma is evolving rapidly, and now needs to balance not only the standard readouts of toxicity and efficacy, but the newer paradigms of potential long-term remission (even cure), and keeping treatment options “in reserve” (be they small molecule or immunotherapy), to allow the use of optimal sequential therapies for long-term management of what is fortunately becoming more of a chronic disease, than a short-term, dismal prognosis cancer. T-Vec significantly adds to the options within this increasingly complex management challenge for clinicians treating metastatic melanoma.</p> <p>The consequence of TVEC not being approved by NICE is that there will be a set of patients, albeit relatively small, with limited metastatic stage IIIB/C/IV M1a disease denied access to an efficacious, well tolerated treatment potentially able to induce long-term remissions. These patients will instead have to be treated earlier with more toxic small molecule/immunotherapy agents (which cannot then be kept in reserve), which, in fact, have a relatively limited evidence base in this particular group of melanoma patients.</p>	

Role	Comment [sic]	Response
<p>NHS Professional 3</p>	<p>NICE appraisal of T Vec for the treatment of malignant melanoma has failed to take into consideration the potential value of a treatment that has a unique mechanism of action, and which is the most convincing evidence of a successful therapeutic cancer vaccine ever published. I feel strongly that T vec should be made available for suitable patients with malignant melanoma and provide a routine treatment option for defined specific patients. Although immunotherapy such as Provenge in prostate cancer have been associated with improved survival, only T Vec has provided clear radiological evidence of abscopal tumour regression and improved disease control. The committee stated that a new agent with a novel mechanism of action and improved tolerability would be valuable for patients with stage IIIB/c IV M1a melanoma, if it could be shown to be as clinically effective as other immunotherapy agents (in this case ipilimumab (Ipi)).</p> <p>This is a flawed argument in that:</p> <ol style="list-style-type: none"> 1. T Vec cannot be regarded to be a direct comparator with ipi in terms of their biology, patient stage and selection, mode of action and especially in view of the massively contrasting toxicity profiles. 2. T-vec creates a new treatment option wholly unrelated to ipi or other drugs, and this is its value rather than its limitation 3. There is clear and defined unmet need in these stages of an inevitably aggressive malignancy, despite the availability of ipi. 4. There are enormous quality of life benefit for T vec over immune checkpoint inhibitors, and no life threatening toxicities 5. Not having T vec as a treatment option either gives patients no treatment option or forces premature use of toxic and expensive drugs such as ipi, and downstream reduces options for treatment if disease progresses. At this point the patient may not be fit enough for ipi. 6. Ipi therapy is associated with hospitalisation and fatalities, even now in an era of routine use and considerable experience by specialist in large centres. T vec has never shown a comparable adverse toxicity profile. 7. The numbers of patients suitable for T vec nationally per annum are modest 8. Patient choice has to be respected and an integral component of optimal disease management 	<p>Comment noted. The committee agreed that intra-lesion injections are an innovative approach to the treatment of melanoma, although the marketing authorisation did not support the systemic action of talimogene laherparepvec. However, the committee could not identify any specific health related benefit that had not already been captured in the QALY calculation (see FAD section).</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable.</p>

Role	Comment [sic]	Response
<p>NHS Professional 4</p>	<p>The optimum management of non-resectable stage III/IVA melanoma remains unclear, with few options having been specifically studied in this setting. T-VEC is an exception, with the phase III OPTIM study having included a well defined and large cohort of patients in this setting. The efficacy and toxicity were both very favourable, demonstrating that T-VEC provides a valuable option in this setting. Indeed, the panel agreed that “the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for patients with metastatic melanoma.</p> <p>The submission sought to compare T-VEC principally with ipilimumab, following a previous scoping exercise. There have been no direct comparisons between T-VEC and ipilimumab, and as such any comparisons were indirect. In addition the activity of ipilimumab in this setting is not fully known, as few patients with this stage disease were included in large phase trials. Thus, the difficulty in comparing the two agents was predominantly due to a lack of data for ipilimumab in this setting, rather than for T-VEC.</p> <p>The modelling in the submission included an adjustment to ipilimumab’s efficacy in this setting. The need for such an adjustment is based at least partly on the assumption that lower volume disease may respond more favourably compared to higher volume later stage disease. One way of at least partly addressing this would be to compare with the efficacy of ipilimumab in the adjuvant setting where residual disease is at a minimum. In a recent large adjuvant study of ipilimumab (i.e. resected stage III disease), the 3-year recurrence-free survival was 46.5% in those treated with ipilimumab and 34.8% in the placebo arm (1). This implies that recurrence rate was reduced from 65.2% to 53.5%, i.e. by 11.7%. In other words recurrences were “prevented” in about 18% of those at risk, a similar degree of clinical efficacy to that seen in advanced disease, where approximately 20% of patients gain benefit (respond to treatment or have prolonged stable disease). OS data has not yet been reported.</p> <p>Notably, in the adjuvant study the 2-year relapse free rate was 51.5% (ipilimumab) compared to approximately 40% for patients with Stage III/IVA disease receiving T-VEC in OPTIM. Considering the worse prognosis of patients in the latter group, it would appear unlikely that ipilimumab could be significantly more active in T-VEC in the unresectable stage III/IVA groups.</p>	<p>Comment noted.</p> <p>The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable.</p>

Role	Comment [sic]	Response
Patient organisation	Melanoma patients are extremely disappointed in the decision. TVEC offers an important, novel, additional option in this small cohort of patients. NICE's position is that TVEC should not be recommended because there is a lack of data for TVEC's comparator treatments if they are being used in the earlier stage disease where TVEC is positioned. NICE themselves acknowledge that TVEC has an improved tolerability profile than later lines of treatment. Patients and clinicians need to have access to as many innovative treatments as possible.	The FAD recommends talimogene laherparepvec as a treatment option when treatment with systemically administered immunotherapies is not suitable

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

**Talimogene laherparepvec for treating metastatic
melanoma**

Response to appraisal consultation document

Prepared by:



13 April 2016

File name	Version	Contains confidential information	Date
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Executive Summary

We have carefully reviewed the Committee's consideration of the evidence on talimogene laherparepvec for treating metastatic melanoma. We are extremely disappointed by the conclusions reached and the resulting preliminary guidance not to recommend talimogene laherparepvec. Throughout our submission we have sought to counter the uncertainties in the evidence by consistently applying conservative assumptions in favour of ipilimumab. We have also sought to counter the associated uncertainty in cost effectiveness by offering a significant patient access scheme (PAS) to reduce the drug cost of talimogene laherparepvec. It appears perverse that because of lack of robust evidence for ipilimumab in earlier stage disease, the Committee have penalised talimogene laherparepvec, concluding that it may not be as clinically effective as ipilimumab in this population.

We are committed to working with NICE to address all of the Committee's main concerns and welcome the opportunity to respond to the Appraisal Consultation Document (ACD). Specifically, we address concerns around the suitability of the Korn methodology for patients with earlier stage disease and provide evidence and analyses to demonstrate that the results are robust and conservative in favour of ipilimumab. These analyses consistently support the findings of the Korn methods applied in our initial submission, reinforcing our conclusions that talimogene laherparepvec is at least as clinically effective as ipilimumab in patients with earlier stage disease. Additionally, to further support the case that talimogene laherparepvec is cost effective versus ipilimumab, we demonstrate that talimogene laherparepvec is cost effective versus recognised treatments (dacarbazine (DTIC)) and best supportive care (BSC), but with more favourable incremental cost effectiveness ratios (ICERs) than demonstrated by ipilimumab in previous NICE appraisals against the same treatments. These analyses are important because they provide an alternative to the Korn approach and offer a consistent basis for comparing cost effectiveness across the separate appraisals.

A summary of our responses to the main concerns is presented below followed by detailed responses in sections 1 to 6. Additionally, in section 7 we list a number of factual inaccuracies in the ACD.

We fully anticipate that our responses and the consistency of our findings based on the further analyses presented, will sufficiently address the uncertainties identified by the Committee.

1 The Korn methods, used to evaluate comparative effectiveness in earlier stage disease, are suitable to adjust ipilimumab survival data to the earlier stage population. They are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show talimogene laherparepvec is at least as effective as ipilimumab in the worst-case scenario.

The Committee raised concerns around the applicability of the Korn methods to earlier stage disease although the Evidence Review Group (ERG) was unable to offer an alternative approach. We strongly refute the criticisms raised and show that the Korn method used was sufficiently robust to estimate effectiveness of ipilimumab in patients with earlier stage disease (IIIB-IVM1a). We also reject claims that the

Korn methods overestimated efficacy in favour of talimogene laherparepvec and demonstrate that conversely they were consistently conservative in favour of ipilimumab.

2 Analyses using Korn methods to evaluate comparative efficacy in the broader population of patients including later stage disease, support the case that talimogene laherparepvec is at least as effective as ipilimumab.

Korn methods have been used within previous appraisals and accepted by NICE as a suitable method for evaluation of comparative efficacy in a broader population of patients with stage IIIB-IVM1c disease. Therefore evaluation of comparative efficacy of talimogene laherparepvec and ipilimumab in a broader population directly addresses the limitations raised by the Committee regarding suitability of the Korn methods in an earlier stage population. Analyses conducted in the broader (unlicensed) ITT population from OPTiM, which includes a substantial proportion of later stage patients, showed that talimogene laherparepvec is at least as effective as ipilimumab: median (95% CI) OS was 23.3 (19.5, 29.6) months and 16.5 (14.0, 21.3) months respectively. This adds to the level of certainty that talimogene laherparepvec would also be at least as effective as ipilimumab in earlier stage disease.

3 Analysis using conventional indirect treatment comparison (ITC) methods to compare talimogene laherparepvec with ipilimumab in earlier stage disease also shows that talimogene laherparepvec is at least as effective as ipilimumab; supporting the findings using Korn methods, and providing external validity.

We have conducted a simple ITC of talimogene laherparepvec and ipilimumab in earlier stage disease, assuming (conservatively) that the efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) is the same as the comparator treatments included in the ipilimumab trials (DTIC and gp100). The ITC showed no significant difference in overall survival (OS) between talimogene laherparepvec and ipilimumab in earlier stage disease, with a trend towards a more favourable survival effect for talimogene laherparepvec compared with ipilimumab: hazard ratio (HR) (95% CI) 0.87 (0.53, 1.45) (P=0.61). We consider that this HR represents a conservative estimate of the treatment difference in favour of ipilimumab since our analyses also demonstrate that GM-CSF is at least as effective as DTIC and gp100. This further increases the level of certainty that talimogene laherparepvec is at least as effective as ipilimumab in earlier stage disease.

4. Cost effectiveness analysis show that talimogene laherparepvec is cost effective versus ipilimumab even when using the ERG method for OS extrapolation; provided that it is consistently applied to both treatments.

We believe the Committee is incorrect to state that OS with talimogene laherparepvec could be less favourable than with ipilimumab using the ERG extrapolation method. The ERG method does not appear to have considered the full observed survival times of patients. In addition the ERG did not consistently apply its method to both treatments and as a result misleadingly concluded that talimogene laherparepvec OS could be worse than ipilimumab. The approach we have taken for OS extrapolation aligns with that taken in previous NICE appraisals for ipilimumab and is more clinically plausible than the ERG method which does not represent the

trajectory of melanoma patients. We also demonstrate that if the ERG extrapolation approach is consistently applied to both therapies (as opposed to only talimogene laherparepvec), the difference in OS is at least comparable and that talimogene laherparepvec remains cost effective versus ipilimumab.

5. There is robust evidence of clinical and cost effectiveness of talimogene laherparepvec versus recognised treatments (DTIC) and BSC but with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that talimogene laherparepvec is cost effective versus ipilimumab.

The OPTiM trial provides robust head to head evidence of clinical effectiveness of talimogene laherparepvec versus GM-CSF. Since we have demonstrated that GM-CSF is at least as effective as recognised treatments (DTIC) and BSC, the GM-CSF arm can be used conservatively as a proxy for DTIC and BSC, providing evidence of clinical effectiveness of talimogene laherparepvec versus these treatments. Therefore it is also possible to evaluate the cost effectiveness of talimogene laherparepvec versus DTIC and BSC, to provide a robust within-trial upper bound ICER.

Using this approach, we demonstrate that talimogene laherparepvec is a cost effective option versus DTIC and BSC with ICERs of £23,919 and £24,094 respectively. Importantly, talimogene laherparepvec results in much lower ICERs versus these treatments than those reported for ipilimumab in previous NICE appraisals. The Committee's preferred ICER reported for ipilimumab versus DTIC was £47,900 (TA319) and versus BSC was £42,200 (TA268). This analysis therefore benchmarks the cost effectiveness of talimogene laherparepvec versus the approach previously used as the basis for recommending ipilimumab and adds further certainty to the assessment of the cost effectiveness of talimogene laherparepvec. It additionally shows, with a high level of certainty, that talimogene laherparepvec would also be cost effective in earlier stage patients who are deemed unsuitable for existing immunotherapies like ipilimumab, for whom the only alternatives are treatments such as DTIC and BSC.

It would appear unfair and inconsistent to reject talimogene laherparepvec when it has demonstrated more favourable ICERs versus the same comparators used in previous NICE appraisals for ipilimumab. Therefore, we would like to appeal to NICE precedent, in considering this important cost effectiveness analysis, to ensure a consistent and fair approach that aligns the Committee's decision making with similar comparisons that were considered appropriate within previous ipilimumab appraisals.

Recommending talimogene laherparepvec within this appraisal presents an opportunity to make available a novel oncolytic immunotherapy recognised by the EMA as an innovative first-in-class Advanced Therapy Medicinal Product (ATMP). Talimogene laherparepvec is the only treatment specifically indicated in this earlier stage patient population of high unmet need with evidence of a clinically significant and meaningful OS gain of 25.3 months, a highly favourable safety profile, and long-term OS data out to 5 years.

A negative recommendation will restrict treatment options for these earlier stage patients to other more toxic immunotherapies for which there is limited

evidence of effectiveness in this population.

We believe that the clinical and cost effectiveness case presented for talimogene laherparepvec is sufficiently robust versus ipilimumab. We have also presented the case that talimogene laherparepvec is cost effective versus recognised treatments (DTIC) and BSC, but with much lower ICERs than previously demonstrated by ipilimumab against the same treatments. Further, the PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty in cost effectiveness. We therefore propose that NICE recommend talimogene laherparepvec for routine use in patients with unresectable melanoma that is regionally or distantly metastatic (stage IIIB-IVM1a) with no bone, brain, lung or other visceral disease

1 Suitability of the Korn methods to adjust ipilimumab survival data to earlier stage disease

- The Korn methods are suitable to adjust ipilimumab survival data to earlier stage, non-visceral (IIIB, IIIC and IVM1a) disease: The development of the original Korn model included patients with stage IVM1a disease and there is robust evidence to show that the disease trajectories for unresectable, stage IVM1a and stage IIIB/C are similar.
- It is not correct to suggest that the inclusion of an adjustment for lactate dehydrogenase (LDH) level in the modified Korn method leads to an overestimate of the efficacy of talimogene laherparepvec. Instead it was a conservative approach which increased the estimate of OS for ipilimumab.
- Given the significant logical and clinical inconsistencies associated with the original Korn PFS model, we do not consider it appropriate for use and consider the use of the same modified Korn model for both OS and PFS to be more suitable.
- The Korn models are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show talimogene laherparepvec is at least as effective as ipilimumab in the worst-case scenario.

1.1 Relevance of the Korn models to earlier stage disease

The Committee noted the ERG comments that “*Amgen is to be complemented for the thorough approach to the problem of estimating the effectiveness of talimogene laherparepvec versus ipilimumab in earlier stage disease*”. However, the Committee raised concerns around the suitability of the Korn model for estimating survival in patients with earlier stage, non-visceral disease (IIIB-IVM1a, talimogene laherparepvec licensed population). It is noteworthy that the ERG did not propose an alternative solution to this problem and that the issues raised relate to the limitations of the evidence base of the comparator, ipilimumab, in the licensed population for talimogene laherparepvec.

The original Korn model identified prognostic factors in advanced melanoma based on a meta-analysis of studies in stage IV disease where patients were treated with chemotherapy (Korn et al, 2008). Almost a quarter of these patients had non-visceral, stage IVM1a disease (277/1278 patients, 22%) and therefore the prognostic factors identified (and subsequently used in the modified Korn model) must be considered relevant to earlier stage, non-visceral IVM1a disease. The modified Korn model (NICE TA319, 2014) was derived by modelling the potential prognostic factors, including those from the original Korn publication, in a population of ipilimumab-treated patients, making it highly clinically relevant for adjusting ipilimumab survival data. In this ipilimumab-treated population 11% (57/540 patients) had earlier stage, non-visceral disease (IIIB-IVM1a), predominantly IVM1a disease (Hodi et al, 2010).

We acknowledge that the suitability of the Korn models could be questioned for earlier stage patients with stage IIIB and IIIC disease, however there is strong evidence showing that the disease trajectory for those with stage IIIB/C and IVM1a disease is similar: data from the United States Surveillance, Epidemiology, and End Results (SEER) database in 1682 patients diagnosed with unresectable stage IIIB/C and IVM1a disease suggest that one, two and three year survival rates are similar in those with stage IIIB/C and IVM1a disease (Song et al, 2015):

- 1-year survival rate: 67.2% for stage IIIB/C vs. 64.5% for stage IVM1a
- 2-year survival rate: 42.9% for stage IIIB/C vs. 40.4% for stage IVM1a
- 3-year survival rate: 32.1% for stage IIIB/C vs. 26.4% for stage IVM1a

An analysis of disease trajectory by stage of disease based on the American Joint Committee on Cancer (AJCC) Melanoma Staging Database (Balch et al, 2009) did show differences between stage IIIB/C and IV1a. However, unlike the SEER analysis, this was based on a population which included patients with **resectable disease**, for whom there is a very different prognosis and disease trajectory. Since the proportion of resectable patients is likely to be higher for stage IIIB/C than IVM1a disease, the comparison of survival in these two groups will be confounded by resectability status. Therefore we believe that the SEER database analysis provides the most relevant information on disease trajectory for the talimogene laherparepvec licensed population of patients with **unresectable** disease.

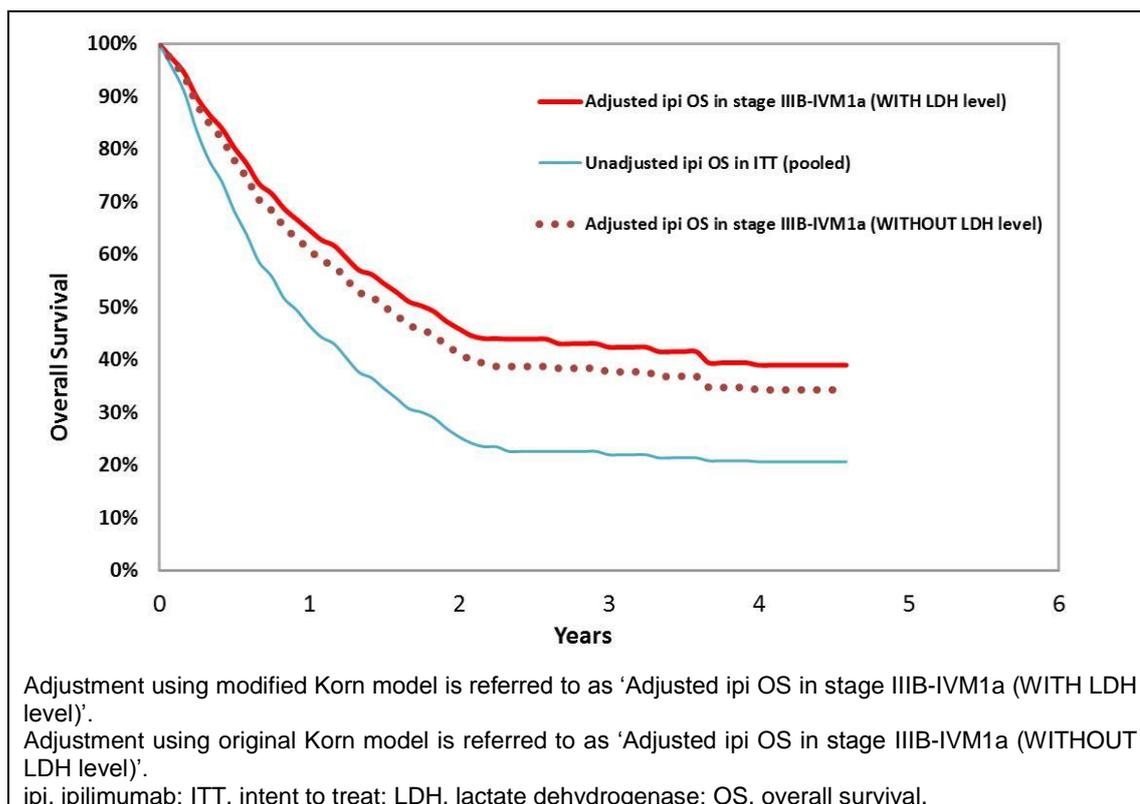
In summary, the development of the Korn models were based on a population which included patients with earlier stage IVM1a disease, and there is robust evidence to demonstrate that the disease trajectories for unresectable, stage IVM1a and stage IIIB/C are similar. **It is therefore reasonable to consider that the Korn models are appropriate for patients with earlier stage, non-visceral stage IIIB/C and stage IVM1a disease.**

1.2 Impact of LDH in the modified Korn model

“It [the Committee] also questioned the inclusion of an adjustment for LDH level in the modified Korn method, as this is of limited relevance for people with stage IIIB, stage IIIC or stage IVM1a disease. Furthermore, the LDH adjustment had the effect of reducing the influence of other prognostic adjustment factors, leading to an overestimate of the efficacy of talimogene laherparepvec compared with ipilimumab”. (Page 25, 4.4).

The Committee questioned the inclusion of LDH in the modified Korn model and its impact on estimation of efficacy. It is not correct to suggest that the use of the modified Korn model including LDH resulted in an overestimate of the efficacy of talimogene laherparepvec. Instead it was a conservative approach in favour of ipilimumab (as opposed to original Korn which does not include LDH) and so reduced the OS treatment difference between talimogene laherparepvec and ipilimumab. In order to address this point, we have compared the adjustment made to ipilimumab OS data based on the modified Korn model including LDH, with the adjustment based on the original Korn model which does not include LDH (see Appendix 9.1 for details). Results are shown in Figure 1.

Figure 1. Comparison of adjusted ipilimumab OS with and without LDH levels



Contrary to the comments in the ACD, the inclusion of LDH was conservative in favour of ipilimumab and did not overestimate the efficacy of talimogene laherparepvec compared with ipilimumab.

1.3 Korn model for PFS

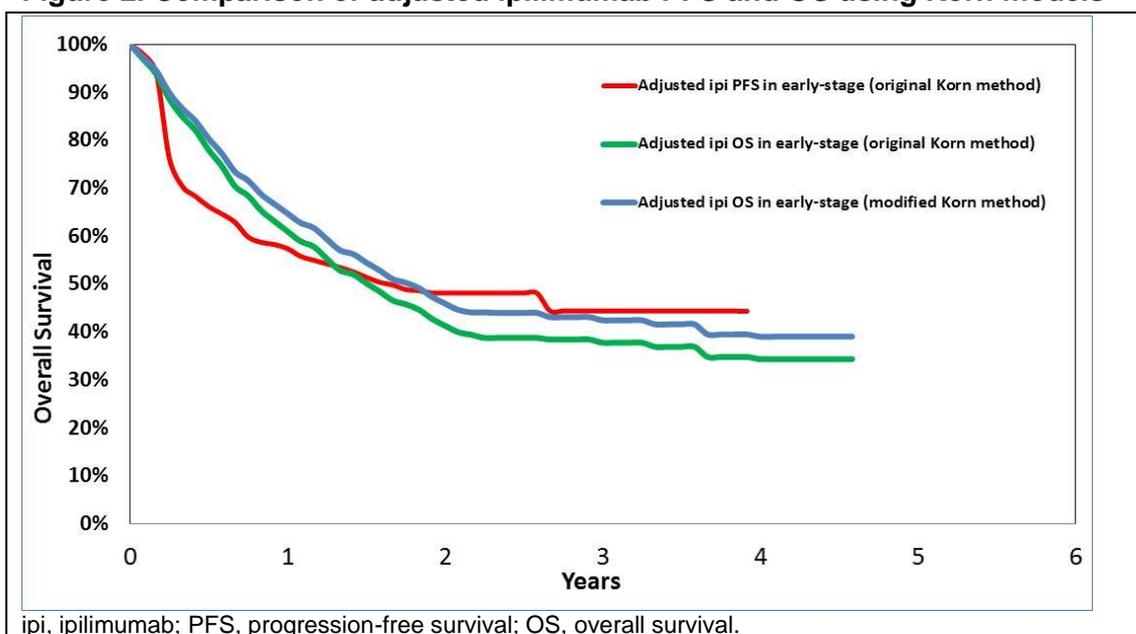
“The ERG suggested that the company’s use of the same modified Korn model for both overall survival and progression-free survival is inappropriate (see section 3.16). The ERG suggested that this is likely to lead to misrepresentation of estimated progression-free survival trends for ipilimumab and substantial additional uncertainty in estimated model outcomes, which in turn will affect the balance between survival time spent in the progression-free and progressed health states”. (Page 17, 3.28)

The Committee raised concerns about the use of the same modified Korn model for both OS and PFS. The modified Korn OS model was used for both OS and PFS given that there was no modified Korn model specific to PFS based on the same data source (i.e. ipilimumab-treated patients). Given the high expected correlation between PFS and OS, the same adjustment factors for PFS as for OS (based on the OS modified Korn model) were used (Flaherty et al, 2014).

A separate PFS model is available in the original Korn publication. However, we do not consider it reasonable to use the original Korn PFS model. Indeed the authors of the Korn publication note that the PFS model is problematic, given the between-trial variability in PFS rates and differences in assessment frequencies, and caution against using it stating “we do not recommend comparisons with the whole historical Talimogene laherparepvec for treating metastatic melanoma [ID508]

control PFS curve” (Korn et al, 2008). We have used the original Korn PFS model to adjust the ipilimumab PFS data (to the talimogene laherparepvec earlier stage population) and note that indeed there are significant logical inconsistencies which arise. Figure 2 shows the adjusted ipilimumab PFS curve using the original Korn PFS model. The adjusted PFS curve is above the adjusted OS curve (over the first 2 months and again after 16 months using original Korn model, or 21 months using modified Korn model) which is not clinically plausible. Appendix 9.2 provides details of the adjustment.

Figure 2. Comparison of adjusted ipilimumab PFS and OS using Korn models



In summary, given the significant logical and clinical inconsistencies associated with the original Korn PFS model, we do not consider it appropriate and instead consider the use of the same modified Korn model for both OS and PFS (as was done in the company submission) to be a more reasonable approach as it has greater clinical plausibility.

1.4 Korn methods are conservative in favour of ipilimumab

In our submission we presented a range of estimates from best case to worst case and claimed that talimogene laherparepvec in the latter scenario was at least comparable to ipilimumab. The worst-case (two-step Korn method) scenario was highly conservative, attributing to ipilimumab an improved treatment effect in earlier stage disease, despite the absence of evidence to show that the treatment effect of ipilimumab is greater in earlier stage patients than it is in the overall population. Specifically, we selected the best possible treatment effect for ipilimumab in earlier stage disease from the previously untreated and previously treated RCTs (CA184-024 and MDX010-20): this was an OS HR of 0.47 for ipilimumab (Hodi et al, 2010) (Table 1). We used this rather than the intent to treat (ITT) HR of 0.72 (previously untreated) and HR of 0.64 (previously treated) despite the authors stating that the effect of ipilimumab on OS was independent of stage of disease (Hodi et al, 2010). Importantly, the OS HR appears worse for earlier stage disease compared with the

overall population in the previously untreated ipilimumab trial (Robert et al, 2011) and we ignored this, which was most conservative, in our two-step Korn calculations.

Table 1. Ipilimumab OS RCT data

Therapy (RCT)	ITT population OS HR (95% CI)	Earlier stage population (IIIB, IIIC and IVM1a) OS HR (95% CI)
Ipilimumab previously untreated patients (CA-184-024) (Robert et al, 2011)	0.72 (0.59, 0.87)	0.83 ^a Note: <20% of patients had earlier stage metastatic disease
Ipilimumab previously treated patients (MDX010-20) (Hodi et al, 2010)	0.64 (0.49, 0.84)	0.47^b (0.27, 0.82) Note: 10.7% of patients had earlier stage metastatic disease
^a Calculated based on the weighted average of HRs for M0 (Stage IIIB and IIIC) and M1a reported in Robert et al, 2011; 95% CI is not estimated ^b Based on subgroup M0 (Stage IIIB and IIIC), M1a and M1b reported in Hodi et al, 2010. CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival; RCT, randomised controlled trial.		

Therefore, where assumptions were required for the Korn analysis, these were consistently conservative in favour of ipilimumab and further support the claim that talimogene laherparepvec is at least as effective as ipilimumab in the worst-case scenario.

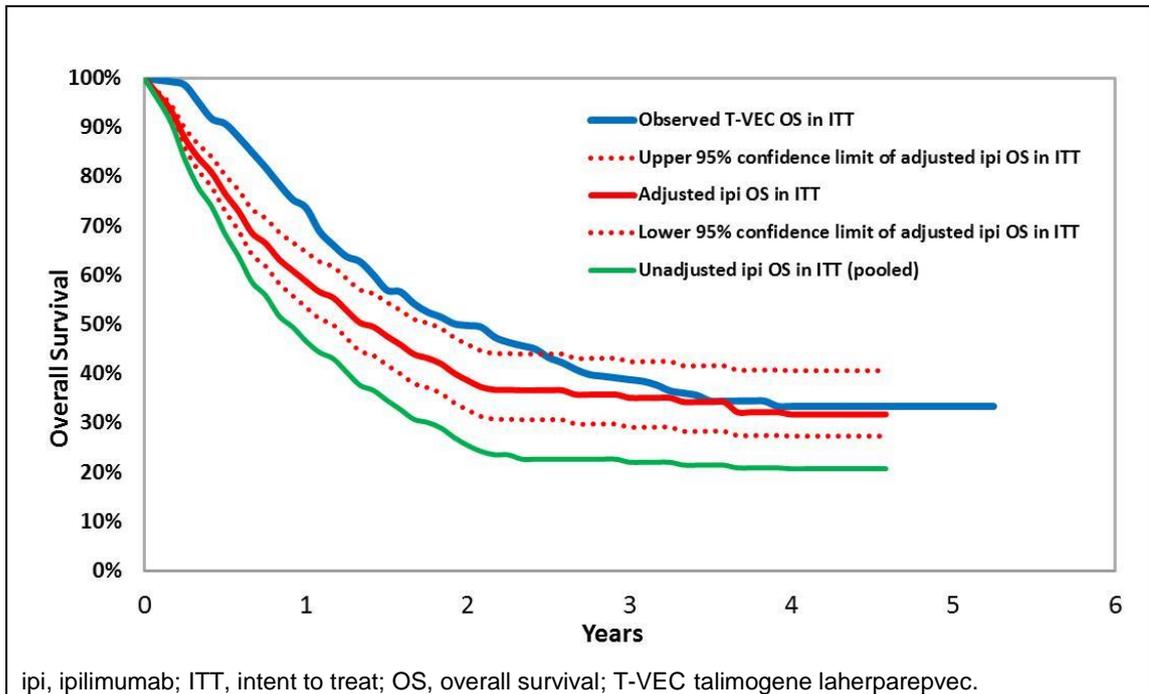
2 Analyses using Korn methods to compare talimogene laherparepvec with ipilimumab in the broader population of patients including later stage disease

- Korn methods have been used within previous appraisals and accepted by NICE as a suitable method for evaluation of comparative efficacy in a broader population of patients with stage IIIB-IVM1c disease.
- Therefore evaluation in the broader OPTiM ITT (stage IIIB-IVM1c) population which includes a substantial proportion of later stage patients, removes the criticisms raised by the Committee regarding suitability of the Korn methods.
- Analyses conducted in this broader population also showed that talimogene laherparepvec is at least as effective as ipilimumab.
- This adds to the level of certainty that talimogene laherparepvec would also be at least as effective as ipilimumab in earlier stage disease, given that talimogene laherparepvec efficacy is greater in this population.

We have demonstrated in the preceding section that the Korn model is applicable to earlier stage disease and that talimogene laherparepvec is at least as effective as ipilimumab in its licensed population. In this section, we perform important analyses in a population where the Korn models are more suitable and relevant: the OPTiM ITT (stage IIIB-IVM1c) population which includes a substantial proportion (44%) of later stage disease patients (IVM1b/c). Although talimogene laherparepvec is not licensed for later stage patients, such a comparison helps address concerns regarding clinical parity of the two agents. Details of methods for this analysis using the modified Korn approach are presented in Appendix 9.3.

Figure 3 shows that OS for talimogene laherparepvec in the ITT population is at least as favourable as the adjusted OS for ipilimumab in the same patient population using the modified Korn method: median (95% CI) OS was 23.3 (19.5, 29.6) months for talimogene laherparepvec and 16.5 (14.0, 21.3) months for ipilimumab.

Figure 3. Comparison of OS for talimogene laherparepvec and ipilimumab in the broader population (OPTiM ITT) using modified Korn method



This analysis in the broader population of patients (including later stage disease) supports the case that talimogene laherparepvec is at least as effective as ipilimumab.

3 Analysis using conventional ITC methods to compare talimogene laherparepvec with ipilimumab in earlier stage disease

- **We present an analysis showing that GM-CSF is at least as clinically effective as DTIC and gp100 regardless of disease stage.**
- **Assuming (conservatively) equivalence of GM-CSF with DTIC and gp100 then allowed a simple ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease.**
- **The results of the ITC showed a trend towards a more favourable survival effect for talimogene laherparepvec although there was no statistically significant difference in OS for talimogene laherparepvec compared with ipilimumab in earlier stage disease: HR (95% CI) 0.87 (0.53, 1.45) (P=0.61).**
- **Analysis using ITC methods to compare talimogene laherparepvec with ipilimumab in earlier stage disease shows that talimogene laherparepvec is at least as effective as ipilimumab. The ITC provides an alternative approach to that of Korn, thereby providing external validity to the previous findings.**

Given the Committee concerns regarding the use of the Korn models, we have now conducted an ITC which provides an alternative to the Korn model for evaluation of talimogene laherparepvec versus ipilimumab in the talimogene laherparepvec licensed population (stage IIIB-IVM1a disease). This is also noted in the ERG report where it is stated that an indirect evidence synthesis may have been appropriate to compare talimogene laherparepvec and ipilimumab if the OPTiM comparator had been a recognised therapy rather than GM-CSF.

We first demonstrated that GM-CSF is at least as effective as DTIC and gp100. This then allowed a simple ITC of talimogene laherparepvec and ipilimumab in earlier stage disease, assuming (conservatively) that the efficacy of GM-CSF is the same as that of DTIC and gp100.

3.1 Analyses demonstrating that GM-CSF is at least as effective as recognised treatments (DTIC) and BSC

We conducted an analysis of the clinical effectiveness of GM-CSF compared with DTIC and BSC. Thirty three studies evaluating DTIC, GM-CSF or gp100 were identified from the company systematic literature review. However, the disconnected network of evidence constructed from these studies showed that a network meta-analysis (NMA) of GM-CSF, DTIC and gp100 was not possible. Therefore the modified Korn methodology (as described in our company submission) was applied to adjust DTIC and gp100 OS data to the OPTiM GM-CSF population, in order to show that GM-CSF is at least as effective as recognised treatments (DTIC) and BSC (gp100).

Given concerns around the Korn methodology in earlier stage disease and in order to demonstrate robustness of results, this analysis was performed adjusting the DTIC and gp100 data across all stages of disease including later stage disease:

- to the OPTiM GM-CSF earlier stage disease population (IIIB-IVM1a)
- to the OPTiM GM-CSF ITT population (stage IIIB-IVM1c)
- to the OPTiM GM-CSF later stage disease population (IVM1b/c).

Appendix 9.5 details the implementation of the modified Korn adjustment.

We employed the same study selection criteria as those used for the comparison of talimogene laherparepvec with ipilimumab in our submission, to identify relevant data for the comparison of GM-CSF with DTIC and gp100, i.e. those which were phase 3 RCTs and which reported mature OS data. Table 2 summarises the six trials that were identified and included in this analysis (Appendix 9.4 provides further detail of study inclusion and exclusion in a PRISMA flow diagram).

Table 2. Trial data used for efficacy comparison of GM-CSF vs DTIC and gp100

Therapy	Trial	Description	OS data used
GM-CSF	OPTiM (Andtbacka et al, 2015)	Phase 3 RCT comparing talimogene laherparepvec with GM-CSF in patients with unresectable stage IIIB-IV melanoma	GM-CSF arm (N=141 in ITT population)
DTIC	CA184-024 (Robert et al, 2011)	Phase 3 RCT comparing ipilimumab plus DTIC with DTIC monotherapy in previously untreated metastatic melanoma patients	DTIC monotherapy arm (N=252)
	BRIM-3 (McArthur et al, 2014; Chapman et al, 2011)	Phase 3 RCT comparing vemurafenib with DTIC in previously untreated stage IIIC or IV melanoma positive for the BRAF ^{V600} mutation	DTIC monotherapy arm (N=338)
	BREAK-3 (Hauschild et al, 2012; Hauschild et al, 2014; Grob et al, 2014)	Phase 3 RCT comparing dabrafenib with DTIC in patients with BRAF ^{V600E} mutation positive metastatic melanoma	DTIC arm (N=63)
	NCT01359956 (Daponte et al, 2013)	Phase 3 RCT comparing fotemustine plus DTIC with DTIC monotherapy in advanced melanoma (IV)	DTIC monotherapy arm (N=70)
gp100	MDX010-20 (Hodi et al, 2010)	Phase 3 RCT comparing ipilimumab with gp100 in previously treated metastatic melanoma patients	gp100 arm (N=136)

GM-CSF, granulocyte-macrophage colony-stimulating factor; DTIC, dacarbazine; OS, overall survival; RCT, randomised controlled trial.

Comparisons of OS for GM-CSF versus DTIC and gp100 are presented in Figure 4 and Figure 5. The associated median and mean OS across disease stages is shown in

Table 3. The median and mean OS estimates are consistently more favourable for GM-CSF compared with DTIC and gp100. The mean OS for GM-CSF, even in later stage disease, is higher than DTIC and gp100: 19.7 months (GM-CSF) versus 19.0 months (DTIC) and 14.3 months (gp100). Results from a similar analysis using the original Korn model (Korn et al, 2008) show consistent results and are presented in Appendix 9.6.

Figure 4. OS comparison of GM-CSF versus DTIC (modified Korn)

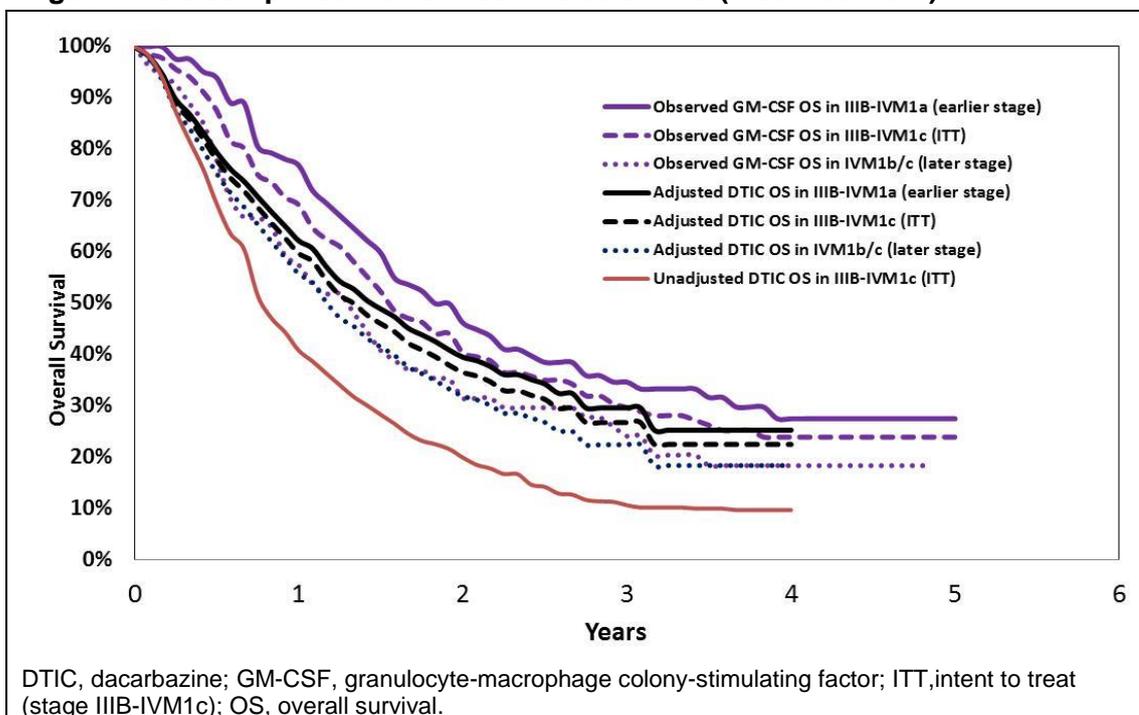


Figure 5. OS comparison of GM-CSF versus gp100 (modified Korn)

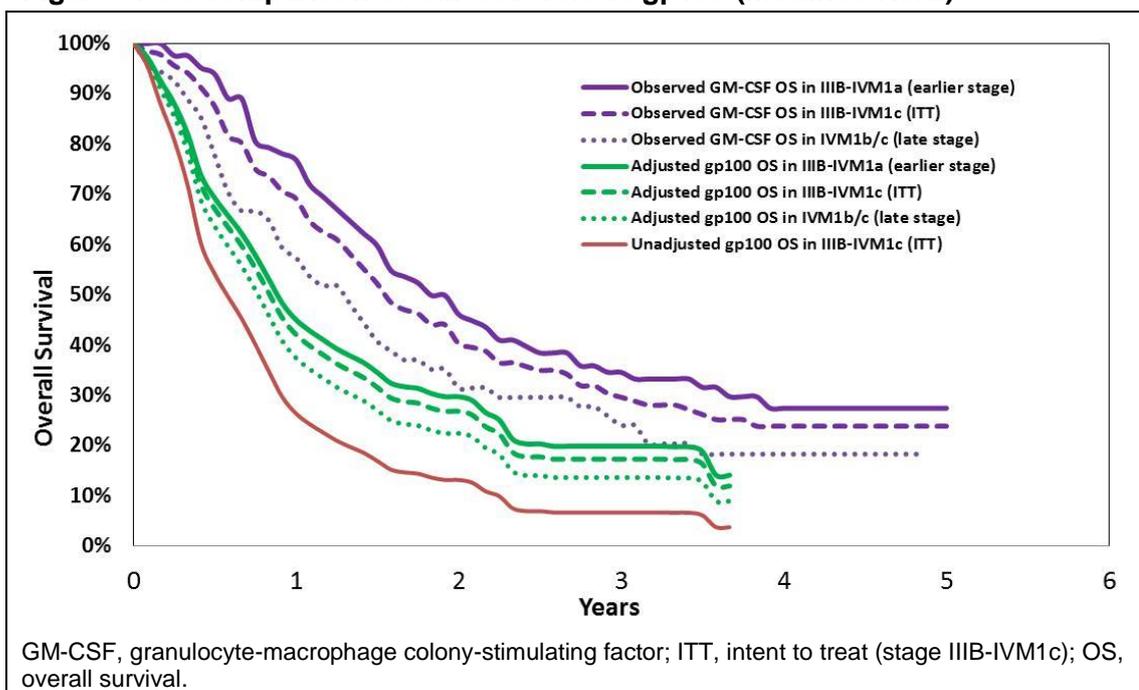


Table 3. Median and mean OS for GM-CSF, DTIC and gp100

	GM-CSF	DTIC		gp100	
	Unadjusted OS (months)	Unadjusted OS (months)	Adjusted OS (months)	Unadjusted OS (months)	Adjusted OS (months)
OPTiM earlier stage disease (IIIB-IVM1a)					
Median	21.5	–	17.3	–	10.6
Mean (95% CI) (AUC)^a	25.4 (20.9, 29.2)	–	21.8 (18.1, 25.3)	–	17.0 (13.2, 21.1)
OPTiM ITT (IIIB-IVM1c)					
Median	18.9	9.3	16.0	6.4	10.1
Mean (95% CI) (AUC)^a	23.1 (19.8, 26.3)	14.5	20.7 (18.2, 23.2)	10.8	16.0 (13.2, 18.9)
OPTiM later stage disease (IVM1b/c)					
Median	15.9	–	14.1	–	9.2
Mean (95% CI) (AUC)^a	19.7 (14.3, 24.5)	–	19.0 (18.2, 19.8)	–	14.3 (13.3, 15.6)
^a To make the mean (AUC) comparison meaningful, the shorter available time period (44 months, which is the gp100 trial length) was used AUC, area under the curve; DTIC, dacarbazine; GM-CSF, granulocyte-macrophage colony-stimulating factor; ITT, intent to treat; OS, overall survival					

In summary, GM-CSF is at least as clinically effective as DTIC and gp100 (previously accepted to be equivalent to BSC by NICE) regardless of disease stage.

3.2 ITC of talimogene laherparepvec versus ipilimumab

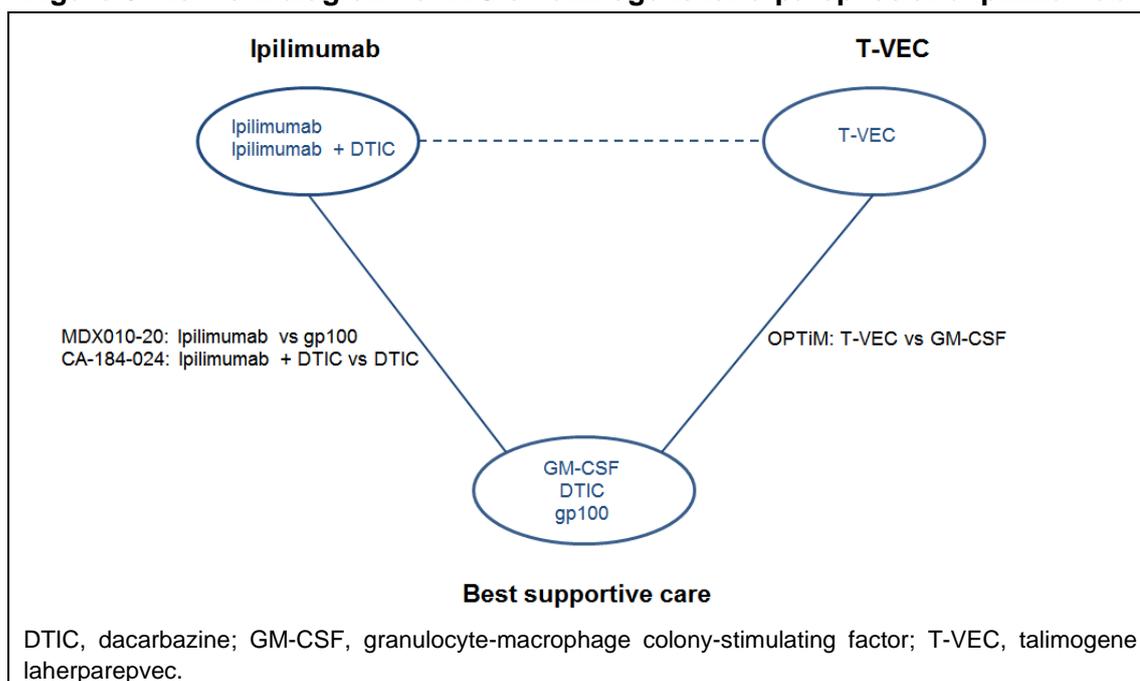
We performed a simple ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease, assuming (conservatively) that the efficacy of GM-CSF is the same as that of DTIC and gp100 (based on the analysis presented in Section 3.1).

The ITC is based on the same RCT data that were used in our company submission to compare OS of talimogene laherparepvec versus ipilimumab, namely data from:

- OPTiM for talimogene laherparepvec (final analysis)
- CA-184-024 for ipilimumab (previously untreated patients)
- MDX010-20 for ipilimumab (previously treated patients)

The network diagram for the ITC is shown in Figure 6.

Figure 6. Network diagram for ITC of talimogene laherparepvec and ipilimumab



In order to conduct the ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease, the following assumptions (with justification) were made:

- Ipilimumab in previously treated patients is equivalent to ipilimumab in previously untreated patients; accepted by NICE (NICE TA319, 2014)
- Ipilimumab + DTIC is equivalent to ipilimumab monotherapy; accepted by NICE (NICE TA319, 2014)
- GM-CSF is equivalent to DTIC and gp100; based on Korn analysis across all stages (section 3.1)

A summary of data used in the ITC analysis, together with calculations performed, is presented in Table 4.

Table 4. Data used in ITC analysis of talimogene laherparepvec and ipilimumab in earlier stage disease

Study	Comparison	OS HR (95% CI)
OPTiM final analysis (IIIB-IVM1a)(Harrington et al, 2015)	Talimogene laherparepvec (N=163) vs GM-CSF (N=86)	<u>IIIB-IVM1a</u> 0.56 (0.40, 0.79)
MDX010-20 Ipilimumab previously treated (M0, M1a and M1b) (Hodi et al, 2010)	Ipilimumab (N=15 M0/M1a, N=22 M1b) vs gp100 (N=15 M0/M1a, N=23 M1b)	<u>M0, M1a and M1b^a</u> 0.47 (0.27, 0.82)
CA-184-024 Ipilimumab previously untreated (M0/M1a) (Robert et al, 2011)	Ipilimumab + DTIC (N=43) vs DTIC (N=51)	M0: 0.36 (0.07, 1.82) ^b M1a: 0.91 (0.53, 1.57) ^b <u>M0/M1a</u> 0.83 (0.50, 1.39) ^c

Study	Comparison	OS HR (95% CI)
Ipilimumab combined RCT data (MDX010-20 and CA-184-024)	Ipilimumab (N=80) vs BSC (DTIC or gp100) (N=89)	0.64 (0.44, 0.93)^d
^a HR not reported for M0/M1a only, therefore it was necessary to use the HR for M0/M1a/M1b to represent earlier stage disease ^b HR and 95% CI calculated from the published log hazard ratio and 95% CI in Robert et al, 2011. ^c Calculated based on the weighted average of HRs for M0 and M1a (as shown in Table 4-25 of our company submission) using inverse variance weighting. ^d Calculated based on the weighted average of ipilimumab HRs from MDX010-20 and CA-184-024 and M1a using inverse variance weighting, i.e. fixed effects meta-analysis. BSC, best supportive care; CI, confidence interval; DTIC, dacarbazine; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; RCT, randomised controlled trial		

The ITC of talimogene laherparepvec and ipilimumab in earlier stage disease was performed using the Bucher method (Bucher et al, 1997), conservatively assuming that GM-CSF is clinically equivalent to DTIC and gp100.

Results are shown in Table 5 and show that talimogene laherparepvec is at least as effective as ipilimumab: the OS HR (95% CI) for talimogene laherparepvec versus ipilimumab was 0.87 (0.53, 1.45) (P=0.61). The confidence interval for the HR is wide, as would be expected given the low number of ipilimumab patients with earlier stage disease.

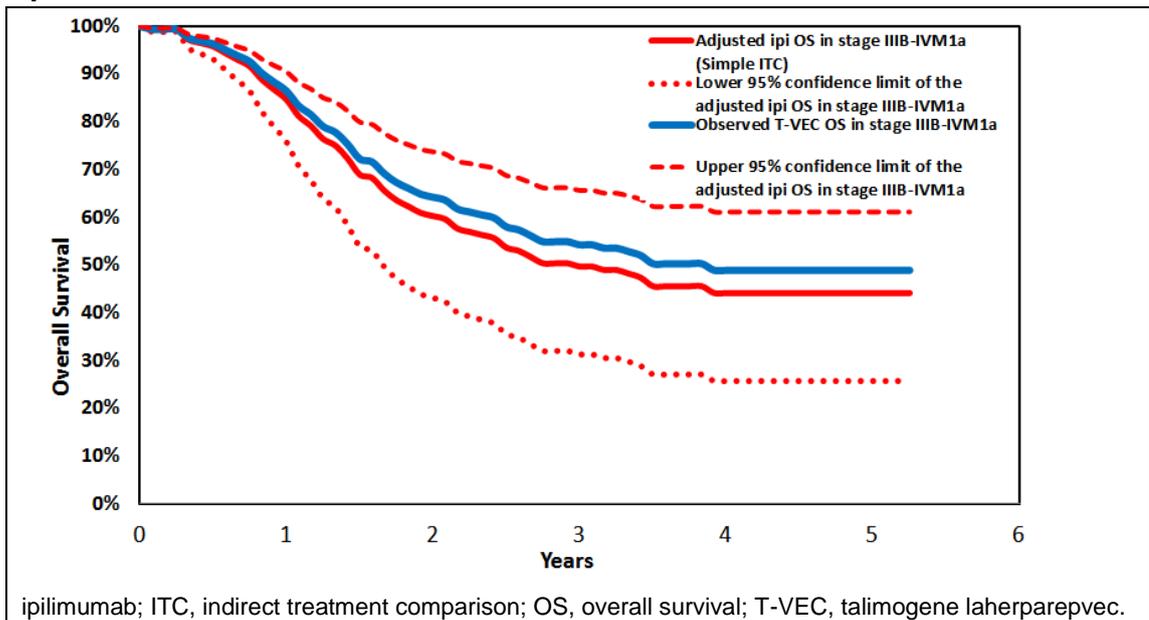
Table 5. Results of ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease

Comparison	OS HR (95% CI)
Talimogene laherparepvec vs GM-CSF	0.56 (0.40, 0.79)
Ipilimumab vs DTIC or gp100	0.64 (0.44, 0.93)
Talimogene laherparepvec vs ipilimumab (ITC)^a	0.87 (0.53, 1.45)
^a Calculated using Bucher method: $HR_{TVEC/IPI} = HR_{TVEC/GMCSF} / HR_{IPI/DTIC(gp100)}$ CI, confidence interval; DTIC, dacarbazine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival	

It is notable that the estimated pooled HR for ipilimumab versus DTIC or gp100 in earlier stage disease (0.64; Table 5) is the same as the HR reported in the ITT population in the previously treated ipilimumab RCT (MDX010-20) (Table 1), therefore providing further evidence that ipilimumab efficacy does not vary by stage.

Figure 7 shows the OS curves for talimogene laherparepvec and ipilimumab in earlier stage disease based on the ITC. Talimogene laherparepvec is at least as clinically effective as ipilimumab. Sensitivity analyses varying the assumptions underlying the ITC are presented in Appendix 9.7 and show similar results.

Figure 7. Comparison of OS curves for talimogene laherparepvec and ipilimumab based on the ITC



In summary, results from a conventional ITC of talimogene laherparepvec and ipilimumab show that talimogene laherparepvec is at least as clinically effective as ipilimumab. This provides external validity and further supports the findings from the Korn models.

Summary of the comparative effectiveness analyses of talimogene laherparepvec versus ipilimumab (sections 1 to 3)

The Korn methods, used to evaluate comparative effectiveness in earlier stage disease, are suitable to adjust ipilimumab survival data to earlier stage disease. They are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show talimogene laherparepvec is at least as effective as ipilimumab in the worst-case scenario. Additionally, analyses using Korn methods to evaluate comparative efficacy in the broader unlicensed population of patients including later stage disease (IIIB-IVM1c), support the case that talimogene laherparepvec is at least as effective as ipilimumab. Notably, analyses show that GM-CSF is at least as effective as DTIC and BSC, supporting the conclusion that the data in the OPTiM trial forms a significant part in assessing the extent to which talimogene laherparepvec benefits patients with earlier stage disease compared with recognised treatments (DTIC) and BSC. Importantly, analysis using conventional ITC, which provides an alternative to the Korn methods to compare talimogene laherparepvec versus ipilimumab in earlier stage disease, shows that talimogene laherparepvec is at least as effective as ipilimumab; supporting the findings from Korn methods, and importantly, providing external validity outside of the Korn methods.

Table 6 summarises the comparative effectiveness evidence presented for talimogene laherparepvec in sections 1 to 3.

In summary, the evidence consistently suggests that talimogene laherparepvec is at least as clinically effective as ipilimumab, despite the conservative approach that has been taken throughout.

Table 6. Evidence of comparative effectiveness of talimogene laherparepvec

Method of comparison	Results	Approach	Level of certainty
Korn methods to compare talimogene laherparepvec vs ipilimumab in earlier stage population (IIIB/C and IVM1a)	Talimogene laherparepvec OS \geq ipilimumab	Highly conservative since we attributed to ipilimumab an improved treatment effect in earlier stage disease, despite the absence of any evidence to show that the treatment effect of ipilimumab is greater in early stage patients than it is in the overall population.	Uncertainties exist due to the lack of robust data for ipilimumab in early stage disease
Korn methods to compare talimogene laherparepvec vs ipilimumab in broader stage population (IIIB-IVM1c)	Talimogene laherparepvec OS \geq ipilimumab	Conservative given that talimogene laherparepvec has also demonstrated a more favourable OS benefit in the earlier stage population but the same is uncertain for ipilimumab.	Lower level of uncertainty given that the use of Korn in broader population including later stage disease is a NICE-accepted method
ITC of talimogene laherparepvec vs ipilimumab in earlier stage population (IIIB/C and IVM1a). Assuming GM-CSF is at least equivalent to DTIC and gp100	Talimogene laherparepvec OS \geq ipilimumab	Conservative given that GM-CSF is at least as effective as DTIC and gp100	ITC provides an alternative to the Korn methods adding confidence and providing external validity to the findings that talimogene laherparepvec is at least comparable to ipilimumab
H2H evidence of talimogene laherparepvec vs GM-CSF in earlier stage population (IIIB/C and IVM1a). Assuming GM-CSF is at least equivalent to DTIC and gp100. GM-CSF used as a proxy to establish talimogene laherparepvec efficacy vs. DTIC and BSC in earlier stage population.	High and durable rate of response, with an unprecedented OS gain of 25.3 months versus GM-CSF	Conservative given that GM-CSF is at least as effective as DTIC and gp100	H2H evidence in subgroup accepted by EMA as sufficiently robust Higher certainty and removes any residual uncertainty associated with the Korn model as it benchmarks the effectiveness of talimogene laherparepvec versus recognised treatments (DTIC) and BSC
BSC, best supportive care; DTIC, dacarbazine; EMA, European Medicines Agency; GM-CSF, granulocyte-macrophage colony-stimulating factor; H2H, head to head; ITC, indirect treatment comparison; OS, overall survival.			

4 Cost effectiveness of talimogene laherparepvec versus ipilimumab

- We believe the Committee is incorrect to state that OS with talimogene laherparepvec could be less favourable than with ipilimumab using the ERG method.
- The ERG approach to OS extrapolation does not represent the trajectory of metastatic melanoma patients and is not clinically plausible. In contrast the Amgen extrapolation more closely matches observed 10 year survival data in melanoma patients and also aligns with the approach for the previous NICE appraisals for ipilimumab.
- This ERG approach is not an appropriate basis on which to inform judgements about the OS of talimogene laherparepvec as it appears to have only considered data up to the last recorded death and ignored the full survival times of patients, thereby incorrectly stating that the company model exponential trend deviated markedly from the final recorded trial data.
- Furthermore, the ERG applied its extrapolation approach only to talimogene laherparepvec rather than consistently applying its method to both treatments and, as a result, misleadingly concluded that talimogene laherparepvec OS could be worse than ipilimumab.
- We demonstrate that as long as the same approach is applied to both therapies (as opposed to only talimogene laherparepvec), the difference in OS is at least comparable and that talimogene laherparepvec still remains cost effective versus ipilimumab.
- Additionally, company assumptions made for the OS extrapolation beyond trial follow-up were consistently conservative, and further support the claim that talimogene laherparepvec is cost effective versus ipilimumab.

The ACD states that based on the ERG approach, the OS with talimogene laherparepvec could be less favourable than with ipilimumab. We refute this and address the issues raised in the ACD around OS extrapolation, showing that the ERG approach lacks clinical validity, is misleading and has been inconsistently applied.

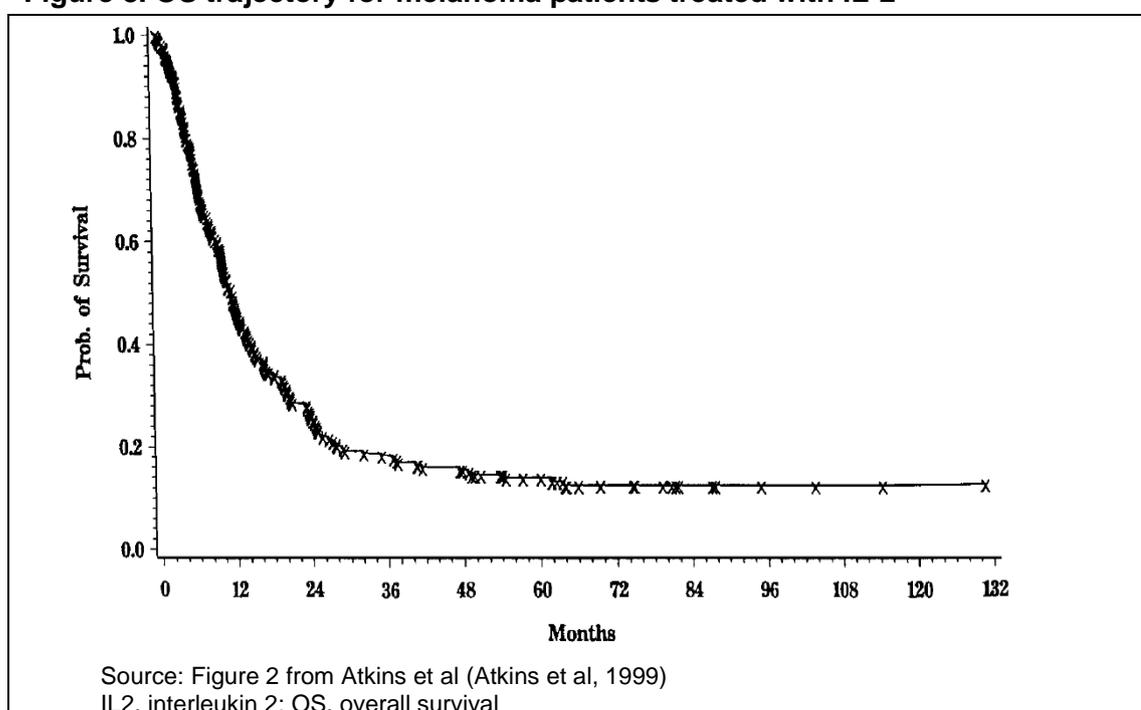
4.1 ERG method of survival extrapolation lacks clinical validity and does not represent the OS trajectory of melanoma patients

The company method used to extrapolate long-term survival for talimogene laherparepvec is consistent with the approach used for the previous NICE appraisals of ipilimumab (NICE TA319, 2014; NICE TA268, 2012). For example, in TA319

(ipilimumab for previously untreated patients) a similar 3-part curve fit for ipilimumab was used consisting of Kaplan-Meier data, followed by a fitted parametric curve and then a curve fitted to long-term registry (AJCC) data. This approach was accepted by the Committee, consequently leading to the positive NICE recommendation for ipilimumab.

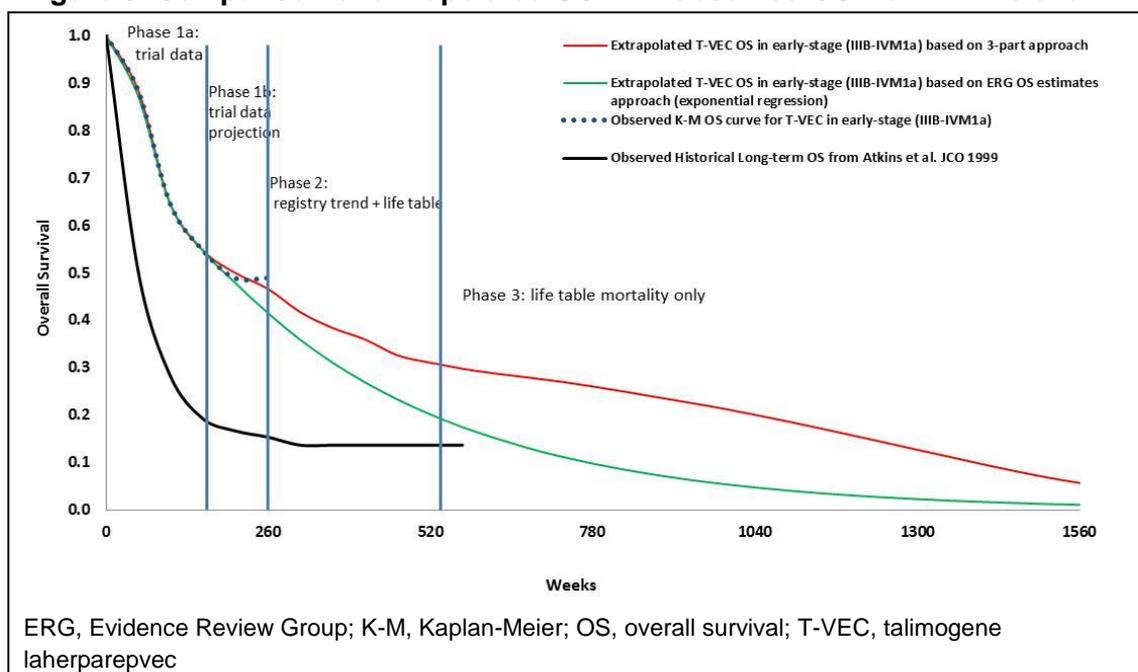
In contrast, the ERG identified a 2-part exponential distribution as the preferred approach to model OS. This not only deviates from the approach for the previous NICE appraisal for ipilimumab but importantly does not represent the long-term survival trajectory of melanoma patients (Figure 8). The observed 10-year OS with Interleukin 2 (IL-2) (Atkins et al, 1999) has often been used as a benchmark to justify the shape of long-term survival for metastatic melanoma and has also been cited in the NICE ipilimumab appraisals (NICE TA319, 2014; NICE TA268, 2012). This data shows that long-term survival is durable with a plateau in the survival curve after 3 years (Figure 8).

Figure 8. OS trajectory for melanoma patients treated with IL-2



We compared the observed survival trajectory from the Atkins IL-2 data with the extrapolated talimogene laherparepvec survival using the ERG approach and the company approach (3-part curve) (Figure 9). The company extrapolation more closely matches the shape of the Atkins IL-2 data which shows that long-term survival after 3 years is durable whereas the shape of the ERG curve without a plateau appears less clinically plausible.

Figure 9. Comparison of extrapolated OS with observed OS from Atkins et al



This demonstrates that the ERG approach to extrapolating long-term survival using an exponential distribution lacks clinical validity and does not represent the trajectory of melanoma patients.

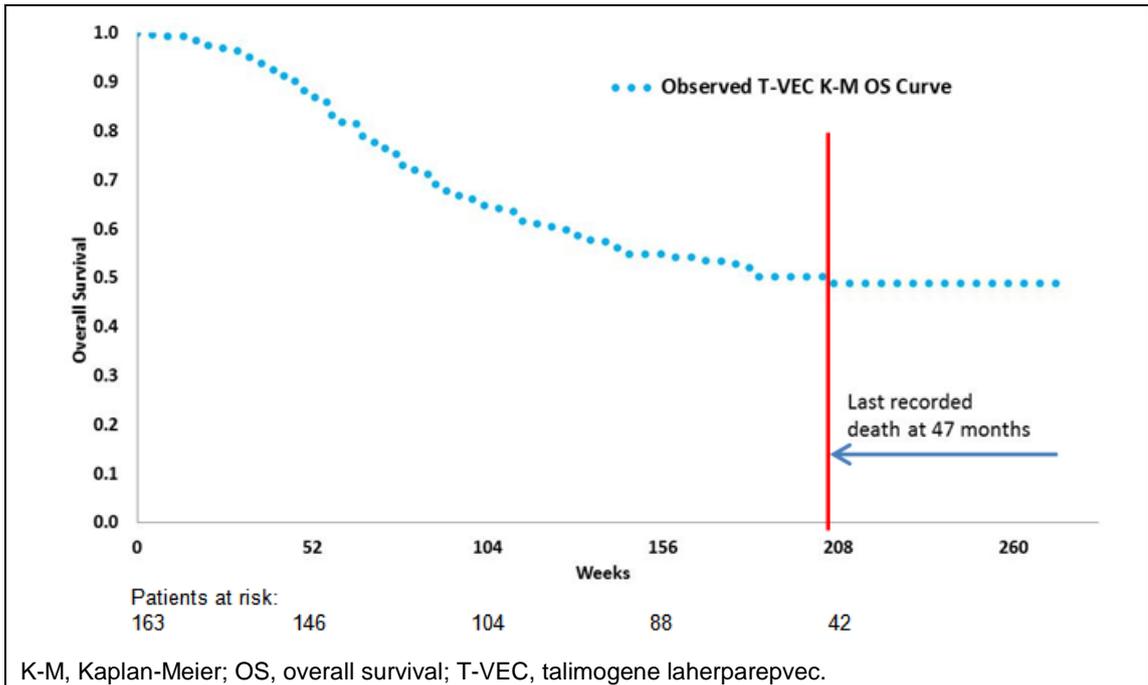
4.2 ERG method of survival extrapolation does not appear to have considered the entire Kaplan-Meier OS curve for talimogene laherparepvec and has not been consistently applied

In the preceding section, we showed that the ERG preferred extrapolation method lacked clinical validity. In this section, we further show that the ERG method is not an appropriate basis on which to inform judgements about the OS of talimogene laherparepvec and the ACD is factually incorrect in stating that the company model exponential trend deviated markedly from the final recorded trial data given that the ERG do not seem to have considered the full Kaplan-Meier data. Importantly, we demonstrate that even if the ERG method were appropriate, the application of it is inconsistent and leads to misleading claims in the ACD.

Representing Kaplan-Meier data only until the last recorded death is not appropriate and the entire Kaplan-Meier OS curve should be considered

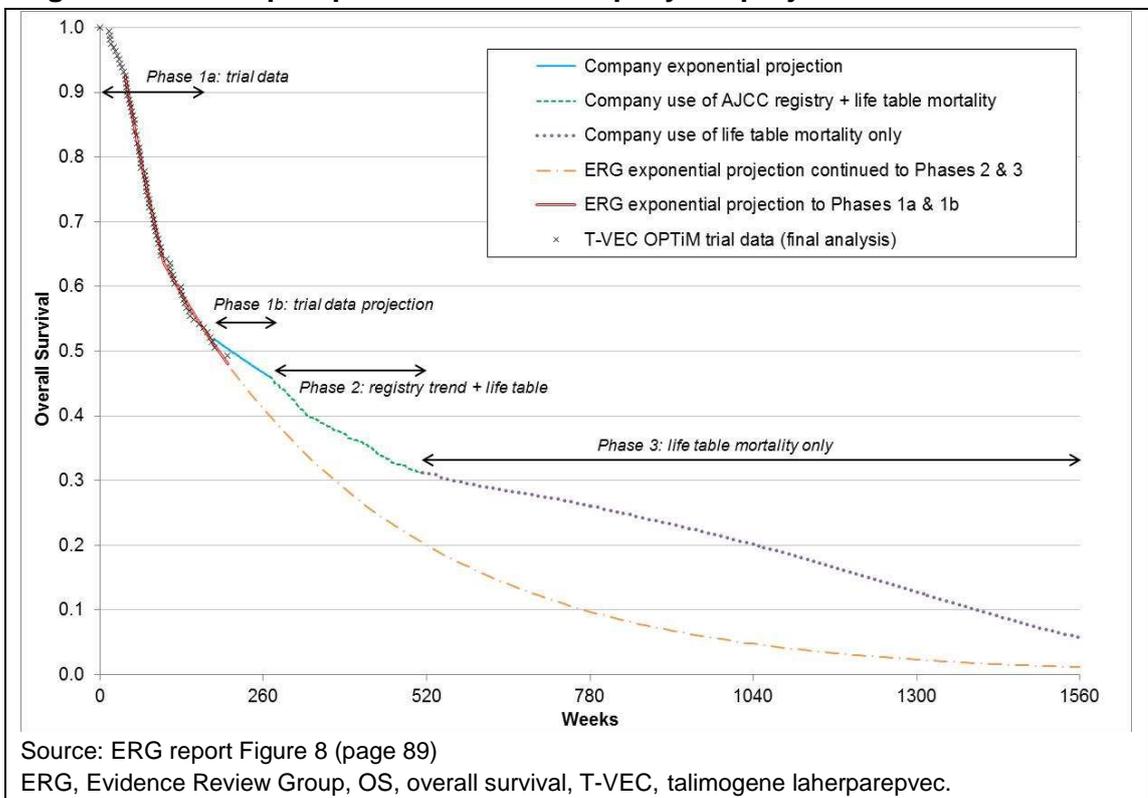
There is long-term OS data for 5 years for talimogene laherparepvec and it is inappropriate to ignore full Kaplan-Meier data when making OS projections as supported by the NICE Decision Support Unit (DSU) document on survival analysis (NICE, 2013). Figure 10 presents the full Kaplan-Meier OS curve (62 months) for talimogene laherparepvec including the number of patients still at risk at various time points and shows that around 40% of patients were still alive post last recorded death (47 months).

Figure 10. Kaplan-Meier OPTiM OS curve for talimogene laherparepvec (stage IIIB-IVM1a disease)



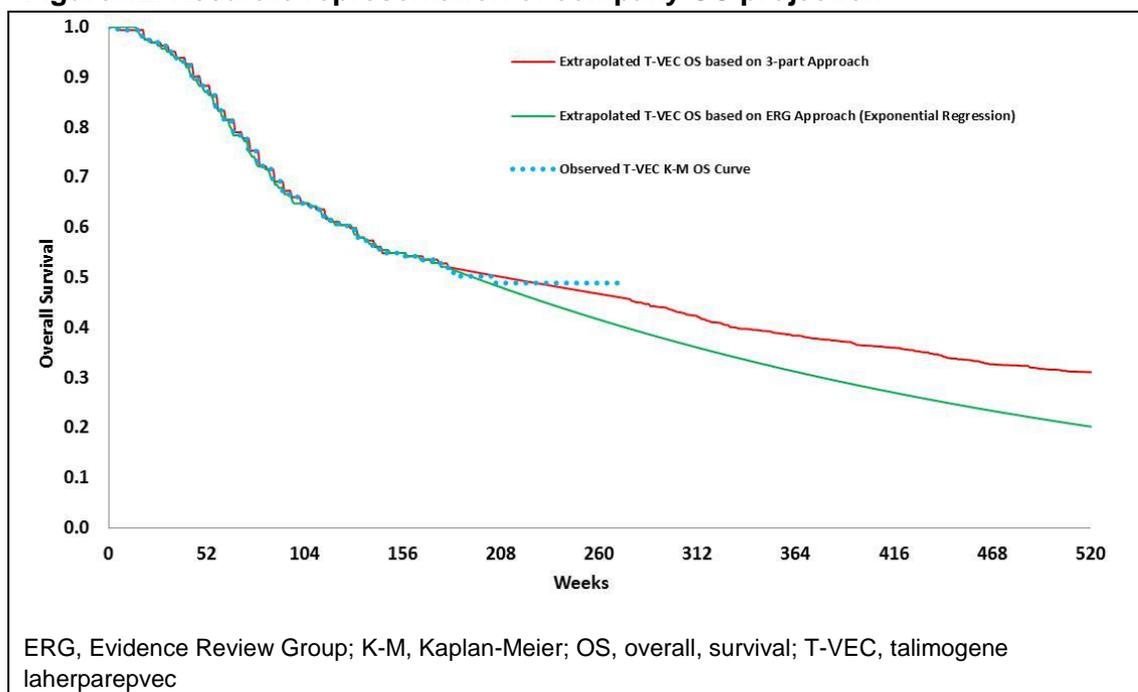
In contrast, the ERG method in Figure 11 (Figure 8 in ERG report) seems to have considered only data up to the timing of the last recorded death (47 months) and ignored observed survival times of patients who were alive and still being followed up post the last observed death until end of trial (62 months).

Figure 11. ERG report presentation of company OS projection



We present the full Kaplan-Meier OS curve together with the company model and the ERG projection in Figure 12. This shows that when considering the full Kaplan-Meier curve, the company exponential trend (labelled as 3-part approach) did not deviate markedly from the final recorded data and indeed was below the final trial data for talimogene laherparepvec (labelled as observed K-M OS curve). Therefore the ACD is factually incorrect in stating that the company model exponential trend deviated markedly from the final recorded trial data.

Figure 12. Accurate representation of company OS projection



The ERG method does not appear to have considered the observed survival times of patients who were still being followed up post the last observed death and is therefore not an appropriate basis on which to inform judgements about the OS of talimogene laherparepvec.

Application of the ERG method to only talimogene laherparepvec leaving the OS for ipilimumab unchanged from the company method is inappropriate

The statement in the ACD that the OS with talimogene laherparepvec could be less favourable than with ipilimumab leading to a substantial effect on the ICER, with the possibility that it would be dominated by ipilimumab (less effective and more costly), is misleading. In this section we demonstrate that the ERG has inconsistently applied its preferred extrapolation approach, applying this only to talimogene laherparepvec leaving the OS for ipilimumab unchanged from the company method.

The ERG estimated the mean OS for talimogene laherparepvec to be 73 months based on their extrapolation instead of 108.5 months based on the company method. However, they left unchanged the mean OS for ipilimumab at 100 months using the company method. This is unreasonable since there is no clinical basis to assume that the company method is an appropriate estimate for the mean OS for ipilimumab in earlier stage non-visceral metastatic disease but not for talimogene laherparepvec.

Indeed the NICE DSU document on survival analysis notes that it is sensible to use the same type of model and not allow the modelled survival for each treatment to follow drastically different distributions. If different types of models are to be used, they should be justified “using clinical expert judgement, biological plausibility and robust statistical analysis” (NICE, 2013).

When consistently applied (as opposed to only talimogene laherparepvec), the ERG preferred method does not result in a lower OS for talimogene laherparepvec compared with ipilimumab. Table 7 presents the results of consistently applying the ERG extrapolation approach to both arms. We were not able to replicate the ERG 2-part exponential model from the information we had been provided, therefore a single exponential model which yields a lower mean OS (64.9 months compared with the ERG method of 73 months) has been used as an approximation of the ERG method to illustrate this point. The results demonstrate that, regardless of the extrapolation method used, the OS benefit for talimogene laherparepvec is at least as favourable as ipilimumab and consequently the impact of different OS extrapolation approaches on the ICER is negligible (Table 8).

Table 7. Comparison of ERG and company OS extrapolation (assuming same extrapolation methodology applied to each therapy)

Extrapolation approach	Mean OS talimogene laherparepvec (undiscounted months)	Mean OS ipilimumab (undiscounted months)	Mean OS difference (undiscounted months)
Modified Korn adjustment			
Single exponential regression (approximation to ERG method)	64.9	37.4	27.5
Company method: 3-part model	108.5	79.1	29.4
Two-step Korn adjustment			
Single exponential regression (approximation to ERG method)	64.9	55.5	9.4
Company method: 3-part model	108.5	100	8.5
ERG, Evidence Review Group; OS, overall survival; T-VEC, talimogene laherparepvec.			

Table 8. Comparison of ICER for talimogene laherparepvec and ipilimumab using ERG and company method for OS extrapolation, PAS price for talimogene laherparepvec

	Single exponential regression £/QALY	Company method £/QALY
Modified Korn adjustment	Dominant	Dominant
Two-step Korn adjustment	Dominant	Dominant
ERG, evidence review group; ICER, incremental cost effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year.		

In summary, the OS for talimogene laherparepvec is at least as favourable as ipilimumab, and talimogene laherparepvec remains cost effective versus ipilimumab even when using the ERG method, provided that it is applied consistently to both treatments.

4.3 Response to other issues around the long-term extrapolation of OS

The Committee questioned some of the assumptions underlying the extrapolation of OS beyond end of trial data in the company submission. We respond to these below and show that the company assumptions are conservative for talimogene laherparepvec.

Sudden change in mortality rate between Phase 1b and Phase 2 extrapolation

The ACD queried the sudden increase in mortality depicted in the shape of the curve for talimogene laherparepvec between Phase 1b and Phase 2 extrapolation (Figure 10 of the ERG report). This increase in mortality is due to the switch from the end of trial to the registry (AJCC) hazards and is a conservative approach. A more clinically plausible assumption would be to assume a smooth transition from the end of trial to registry data; however this would only improve the survival of patients on talimogene laherparepvec. Therefore, we retained the assumption of an increase in mortality in order to produce a conservative estimate of survival for talimogene laherparepvec.

Talimogene laherparepvec remains cost effective regardless of model time horizon

The base case time horizon for the company submission was 30 years, which required assumptions around long term survival. The ACD queried the assumption that long-term survival post 10 years is the same as that of the general population. As discussed in section 4.1 survival curves in metastatic melanoma tend to plateau after 3 years, suggesting that the probability of death is the same for all patients once they survive to this point, regardless of disease progression status (Xing et al, 2010). It would therefore also seem reasonable to assume that the probability for death is the same as that of the general population after 10 years. If we assume a time horizon of 10 years, thereby avoiding the assumption that survival post 10 years is the same as that of the general population, talimogene laherparepvec is still cost effective versus ipilimumab (Table 9). Indeed, talimogene laherparepvec remains cost effective versus ipilimumab assuming a 5 year time horizon. This demonstrates that the cost effectiveness of talimogene laherparepvec is robust and not dependent upon assumptions in the long-term beyond trial data (i.e. 5 years).

Table 9. Cost effectiveness analysis of talimogene laherparepvec versus ipilimumab varying the time horizon, PAS price for talimogene laherparepvec

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Time horizon = 30 years (Base Case)							
Modified Korn							
Ipilimumab	£98,219	4.90	3.57	-	-	-	-
Talimogene laherparepvec	████████	6.66	4.91	████████	1.76	1.34	Dominant
Two-Step Korn							
Ipilimumab	£96,035	6.16	4.61	-	-	-	-
Talimogene laherparepvec	████████	6.66	4.95	████████	0.50	0.35	Dominant
Time horizon = 10 years							
Modified Korn							
Ipilimumab	£90,708	3.40	2.47	-	-	-	-
Talimogene laherparepvec	████████	4.53	3.34	████████	1.14	0.86	Dominant
Two-Step Korn							
Ipilimumab	£90,022	4.23	3.14	-	-	-	-
Talimogene laherparepvec	████████	4.53	3.35	████████	0.30	0.21	Dominant
Time horizon = 5 years							
Modified Korn							
Ipilimumab	£85,054	2.37	1.73	-	-	-	-
Talimogene laherparepvec	████████	3.07	2.27	████████	0.71	0.54	Dominant
Two-Step Korn							
Ipilimumab	£84,627	2.91	2.16	-	-	-	-
Talimogene laherparepvec	████████	3.07	2.27	████████	0.17	0.12	Dominant
ICER, incremental cost effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year							

5 Cost effectiveness of talimogene laherparepvec versus recognised treatments (DTIC) and BSC

- We have demonstrated that GM-CSF is at least as clinically effective as recognised treatments (DTIC) and BSC (gp100) and therefore the OPTiM GM-CSF arm can be used conservatively as a proxy for DTIC and BSC, allowing evaluation of cost effectiveness of talimogene laherparepvec versus these treatments
- Talimogene laherparepvec is highly cost effective versus recognised treatments (DTIC) and BSC with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that talimogene laherparepvec is cost effective versus ipilimumab.
- This analysis benchmarks the cost effectiveness of talimogene laherparepvec versus the approach taken for ipilimumab, removing the uncertainty associated with the lack of evidence for ipilimumab in the earlier stage disease population, and adds further certainty to the assessment of the cost effectiveness of talimogene laherparepvec

The lack of robust data for ipilimumab in earlier stage disease has contributed to uncertainties in estimating the comparative effectiveness for talimogene laherparepvec in this population. We therefore present the cost effectiveness of talimogene laherparepvec versus recognised treatments (DTIC) and BSC (gp100) as another approach to addressing uncertainties surrounding the comparison with ipilimumab. We appeal to NICE precedent (in the appraisal of ipilimumab) to allow consideration of this important cost effectiveness analysis.

The cost effectiveness analysis underpinning the recommendation for ipilimumab, was based on a comparison with DTIC and gp100 (with the latter acknowledged by NICE to be an acceptable proxy for BSC (NICE TA319, 2014; NICE TA268, 2012). The OPTiM trial provides robust head to head evidence of clinical effectiveness of talimogene laherparepvec versus GM-CSF. Given that we have demonstrated GM-CSF to be at least as effective as DTIC and gp100 (BSC), the GM-CSF arm can therefore be used as a conservative proxy for DTIC and BSC, providing evidence of clinical effectiveness of talimogene laherparepvec versus these treatments. Therefore it is also possible to evaluate the cost effectiveness of talimogene laherparepvec versus DTIC and BSC, to provide a robust within-trial upper bound ICER.

An assessment of cost effectiveness of talimogene laherparepvec versus DTIC and BSC was conducted (assuming efficacy of GM-CSF arm of the OPTiM trial but costed as DTIC or assigned zero cost for BSC comparison). Table 10 presents the results of the comparison of talimogene laherparepvec versus DTIC and BSC. Table 11 presents the equivalent results of the comparison of ipilimumab versus DTIC and BSC.

Table 10. Incremental cost effectiveness of talimogene laherparepvec versus DTIC and BSC, PAS price for talimogene laherparepvec

Technology (and comparators)	Total costs £	Total life years	Total QALYs	Incremental costs £	Incremental life years	Incremental QALYs	ICER (£) incremental QALYs
DTIC							
GM-CSF costed as DTIC	£32,687	4.02	2.78	-	-	-	-
Talimogene laherparepvec	████████	6.66	4.76	████████	2.64	1.98	£23,919
BSC							
GM-CSF assigned zero cost	£32,341	4.02	2.78	-	-	-	-
Talimogene laherparepvec	████████	6.66	4.76	████████	2.64	1.98	£24,094
BSC, best supportive care; DTIC, dacarbazine; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALYs quality-adjusted life year.							

Table 11. Comparison of ICERs between talimogene laherparepvec and ipilimumab versus the same comparators, DTIC and BSC

	Talimogene laherparepvec £/QALY	Ipilimumab £/QALY
Versus DTIC	£23,919	£47,900 ^a
Versus BSC	£24,094	£42,200 ^b
^a Source: NICE TA319 (NICE TA319, 2014) ^b Source: NICE TA 268 (NICE TA268, 2012) BSC, best supportive care; DTIC, dacarbazine; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.		

Talimogene laherparepvec is a cost effective option versus recognised treatments (DTIC) and BSC with a high level of certainty, 87.1% versus DTIC and 85.7% versus BSC, at the £30k threshold (cost effectiveness acceptability curves are presented in Appendix 9.8). Importantly, talimogene laherparepvec results in much lower ICERs versus these treatments than ipilimumab. The reported ICER for ipilimumab versus DTIC was £47,900 and versus BSC was £42,200 compared with £23,919 and £24,094 respectively for talimogene laherparepvec. This analysis benchmarks the cost effectiveness of talimogene laherparepvec versus the approach taken for ipilimumab, removing the uncertainty associated with the lack of evidence for ipilimumab in the earlier stage disease population, and adds further certainty to the assessment of the cost effectiveness of talimogene laherparepvec. Additionally, this analysis demonstrates that talimogene laherparepvec is also a highly cost effective and reasonable option for earlier stage disease that is unsuitable for existing immunotherapies (and whose treatment options are limited to DTIC or BSC).

In summary, we have presented important analyses which demonstrate that talimogene laherparepvec is cost effective versus recognised treatments

(DTIC) and BSC and indeed has a more favourable cost effectiveness profile versus these treatments compared with ipilimumab. These further support the findings that talimogene laherparepvec is cost effective versus ipilimumab. Therefore it would be perverse to reject talimogene laherparepvec when it has demonstrated more favourable ICERs versus the same comparators as those reported for ipilimumab. We would like to appeal to NICE precedent in considering this important cost effectiveness analysis, to ensure a consistent and fair approach that aligns with previous ipilimumab appraisals.

6 Additional issues – Post-hoc nature of the licensed subgroup forming the clinical evidence base for talimogene laherparepvec

The Committee noted concerns around the post-hoc nature of the OPTiM subgroup analysis in patients with non-visceral disease which forms the basis of the clinical evidence base for talimogene laherparepvec:

“The ERG expressed concern that the population under consideration was based on and 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 stage IVM1a disease, that are likely to have different disease trajectories”. (Page 12, 3.14)

“The Committee discussed the clinical effectiveness of talimogene laherparepvec. It noted that the trial evidence which underpins the marketing authorisation comes solely from an exploratory post-hoc subgroup of people in the OPTiM study who had non-visceral metastatic melanoma”. (Page 23, 4.3)

Although the specific combination of stage IIIB to IVM1a disease was not pre-specified as a subgroup in OPTiM, subgroup analysis by disease stage was pre-specified (IIIB/C, IVM1a, IVM1b, IVM1c), as acknowledged in Table 7 of the ERG report (NICE ID508, 2016). This pre-specified analysis showed that efficacy was most pronounced in stage IIIB/C and IVM1a disease which led to the licensed indication in earlier stage disease.

The credibility of the disease stage subgroup analyses was fully discussed with the EMA and the EPAR acknowledges that these analyses adhered to the EMA guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013), stating that “robust statistical analyses based on pre-specification of covariate, replication across studies (study 005/05 and 002/03), consistency across endpoints, statistical significance of treatment-by-covariate interaction and biological plausibility of the observed effect” were performed (EMA, 2015).

The main concern raised around the post-hoc nature of the licensed subgroup is that it includes patients with stage IIIB/C disease and patients with stage IVM1a disease who are likely to have different disease trajectories. However, data presented in section 1.1 show that the disease trajectory is similar in those with stage IIIB/C and IVM1a disease (Song et al, 2015).

In summary, although the specific grouping of stage IIIB-IVM1a disease was not pre-specified as a subgroup in OPTiM, analysis by disease stage was pre-specified and adhered to regulatory guidance, and resulted in the approved EMA indication.

7 Factual Inaccuracies

We wish to highlight the following factual inaccuracies within the ACD and propose the recommended corrections as described in Table 12.

Table 12. Factual inaccuracies in the ACD

ACD Section	Factual Inaccuracy	Recommended Correction
2.3	The ACD states 'The acquisition cost of talimogene laherparepvec is £1,670 per 1 ml vial of either 1,000,000 plaque forming units (PFU) per ml or 1,000,000 PFU per ml'	This should be corrected to 'The acquisition cost of talimogene laherparepvec is £1,670 per 1 ml vial of either 1,000,000 plaque forming units (PFU) per ml or 100,000,000 PFU per ml'
3.3, Table 1	Durable response rate, overall response rate and complete response should not be reported at the final data cut off in Table 1. Analysis of these endpoints was pre-specified to occur when no further patients has the possibility of meeting the criteria for response and therefore no change to these outcomes (per the EAC) was possible after the primary data cut off. These endpoints were presented in error at the final data cut in our manufacturer submission and we clarified this point in our response to clarification questions	Remove results for durable response rate, overall response rate and complete response at the final data cut off in Table 1.
3.3	Durable response rate results are reported to come from the final data analysis. As explained above, durable response (per the EAC) was assessed once at the primary data cut-off. Results could not change in later data cut offs.	Change 'Talimogene laherparepvec was associated with a higher durable response rate than GM-CSF based on the final data analysis' to 'Talimogene laherparepvec was associated with a higher durable response rate than GM-CSF'
3.3, Table 1	P-values are reported as '0.0001' for durable response rate and time to treatment failure	P-values should be corrected to '<0.0001' for durable response rate and time to treatment failure
3.4, 3.5	The wording 'more than' is not accurate, e.g. 'more than 50% overall decrease in size', 'increases of more than 5 points', 'more than 1 cycle'.	The wording 'more than' should be replaced by 'at least' or '≥' throughout sections 3.4 and 3.5
3.29	The ACD incorrectly states 'the final analysis of the trial data had not been used in the model'.	This statement should be removed since the final analysis data was used in the company model. We previously noted this point in our response regarding factual inaccuracies in the ERG report.
3.30	The ACD incorrectly states that 'the company model exponential trend deviated markedly from the final recorded trial data'. See section 4.2 for further explanation of this point.	This statement should be removed (together with subsequent statements that rely on this).
4.3	OPTiM efficacy results are described as coming from 'the final data cut' for durable response and complete response. As explained above response-based endpoints (per EAC) were assessed once at	Remove the wording 'final data cut' when referring to OPTiM response-based endpoints.

ACD Section	Factual Inaccuracy	Recommended Correction
	the primary data cut. Results could not change in later data cuts.	
4.3	ACD states 'Furthermore, it is not clear what proportion of the relevant stage IIB -IVM1a population in the ipilimumab trials had injectable lesions that could have been treated with talimogene laherparepvec'	This should be corrected to 'Furthermore, it is not clear what proportion of the relevant stage IIIB -IVM1a population in the ipilimumab trials had injectable lesions that could have been treated with talimogene laherparepvec'
ACD, Appraisal consultation document; EAC, Endpoint Assessment Committee; ERG, Evidence Review Group		

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9 Appendix

9.1 Impact of LDH in the modified Korn model.

The adjustment factors applied to ipilimumab OS data are shown for the original Korn approach (without LDH) and modified Korn approach (with LDH) in Table 13.

Table 13. Adjustment factors for ipilimumab OS data with and without LDH levels

Model	OS equation	Adjustment factor for ipilimumab previously untreated trial (CA184-024)	Adjustment factor for ipilimumab previously treated trial (MDX010-20)
Original Korn Model without LDH level	$\log(\widehat{HR}) = 0.248X_{Gender=Male} + 0.436X_{ECOG=1} + 0.948X_{ECOG=2\ or\ 3} + 0.421X_{Visceral=1} + 0.304X_{Brain\ mets=1}$	0.69 ^a	0.60 ^a
Modified Korn Model with LDH level	$\log(\widehat{HR}) = -0.154X_{Gender=Female} - 0.400X_{ECOG=0} - 0.285X_{Visceral=0} - 0.306X_{Brainmets=0} - 0.782X_{LDH=evalated}$	0.60 ^b	0.53 ^b
<p>The adjustment factor adjusts the worse prognosis of patients in the ipilimumab trials to the baseline characteristics patients had in the talimogene laherparepvec licensed population (non-visceral metastatic disease); the lower the adjustment factor, the higher the estimate of survival for ipilimumab.</p> <p>^a Source: Amgen data on file</p> <p>^b Source: company submission Table 4-24</p> <p>LDH, lactate dehydrogenase; OS, overall survival</p>			

9.2 Korn models to adjust PFS

The implementation of the original Korn adjustment to compare PFS and OS for talimogene laherparepvec and ipilimumab is explained in this section.

Methods

1. The original Korn model for PFS was used to adjust the Kaplan-Meier PFS data for differences between the patient and disease characteristics at baseline using the following baseline prognostic factors:
 - Gender (female vs. male)
 - ECOG performance status (0 vs 1 vs ≥ 2)
 - Age (mean age in years)
2. The original Korn model for OS was used to adjust the Kaplan-Meier OS data for differences between the patient and disease characteristics at baseline using the following four baseline prognostic factors:
 - Gender (female vs. male)
 - ECOG performance status (0 vs 1 vs ≥ 2)
 - Presence of visceral metastases (No vs. Yes)
 - Presence of brain metastases (No vs. Yes)
3. The adjustment factor to adjust the comparator trial to match talimogene laherparepvec patient characteristics was estimated. First, hazard ratios that account for the distributional differences in these factors were estimated. Each comparator trial's baseline distribution values was substituted into the log(HR) equation for the baseline prognostic factors taken from original Korn models for PFS and OS (Korn et al, 2008):

Equation for PFS:

$$\log(\widehat{HR}) = 0.131X_{Gender=Male} + 0.278X_{ECOG=1} + 0.604X_{ECOG=2 \text{ or } 3} - 0.151Age$$

Equation for OS:

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

The same was done for the talimogene laherparepvec licensed population in the OPTiM study. The difference in log(HR)s for the talimogene laherparepvec licensed population and comparator trials ITT population reflect the size of the difference in outcomes due to differences in patient populations. Specifically this reflects the differences in the prognosis of patients between the OPTiM study and the comparator trials.

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

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

The calculated HRs and adjustment factors are presented in Table 14. The adjustment factors adjust the prognosis of patients in the comparator trials to the baseline characteristics patients had in the talimogene laherparepvec licensed population in the OPTiM trial. The lower the adjustment factor, the bigger the upward survival for the ipilimumab.

Table 14. Model Coefficients and Adjustment Factors for PFS based on original Korn PFS model and OS based on Original Korn OS Model in Earlier Stage

Treatment	HR equations	Hazard Ratio	Adjustment factor
PFS (Based original Korn PFS model)			
T-VEC stage IIIB-IVM1a	$\log(\widehat{HR}) = 0.131X_{Male=0.56} + 0.278X_{ECOG1=0.26} + 0.604X_{ECOG23=0} - 0.151Age_{64.5}$	0.0000690	NA
Ipilimumab ITT (previously untreated)	$\log(\widehat{HR}) = 0.131X_{Male=0.61} + 0.278X_{ECOG1=0.29} + 0.604X_{ECOG23=0} - 0.151Age_{57.5}$	0.0002011	0.34
Ipilimumab ITT (previously treated)	$\log(\widehat{HR}) = 0.131X_{Male=0.59} + 0.278X_{ECOG1=0.47} + 0.604X_{ECOG23=0.007} - 0.151Age_{56.8}$	0.0002351	0.29
OS (Based original Korn OS model)			
T-VEC stage IIIB-IVM1a	$\log(\widehat{HR}) = 0.248X_{Male=0.56} + 0.436X_{ECOG1=0.26} + 0.948X_{ECOG23=0} + 0.421X_{visceral=0} + 0.304X_{Brain\ metastases=0}$	1.29	NA
Ipilimumab ITT (previously untreated) ^a	$\log(\widehat{HR}) = 0.248X_{Male=0.61} + 0.436X_{ECOG1=0.29} + 0.948X_{ECOG23=0} + 0.421X_{visceral=0.83} + 0.304X_{Brain\ metastases=0.008}$	1.88	0.69
Ipilimumab ITT (previously treated)	$\log(\widehat{HR}) = 0.248X_{Male=0.59} + 0.436X_{ECOG1=0.47} + 0.948X_{ECOG23=0.007} + 0.421X_{visceral=0.891} + 0.304X_{Brain\ metastases=0.109}$	2.15	0.60
^a in the BMS NICE submission for ipilimumab in previously untreated patients, an OS was derived for monotherapy ipilimumab at 3 mg/kg for the previously untreated study population. The adjustment factor calculated in this analysis was applied to the derived OS data.			
HR, hazard ratio; ITT, intent to treat; NA, not applicable; OS, overall survival; PFS, progression-free survival			

9.3 Modified Korn model to compare talimogene laherparepvec with ipilimumab in the broader population of patients including later stage disease

The implementation of the modified Korn adjustment to compare OS for talimogene laherparepvec and ipilimumab in the OPTiM ITT population (IIIB-IVM1c) is described in this section.

Methods

1. The modified Korn model was used to adjust the Kaplan-Meier data for differences between the patient and disease characteristics at baseline using the following four baseline prognostic factors:
 - Gender (female vs. male)
 - ECOG performance status (0 vs. ≥1)
 - Presence of visceral metastases (No vs. Yes)
 - Presence of brain metastases (No vs. Yes)
 - LDH (Normal vs. Elevated)
2. The adjustment factor to adjust the comparator trial to match talimogene laherparepvec patient characteristics was estimated. First, hazard ratios that account for the distributional differences in these factors were estimated. Each comparator trial's baseline distribution values was substituted into the log(HR) equation for the baseline prognostic factors taken from the modified Korn model (NICE TA319):

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

The same was done for the talimogene laherparepvec licensed population in the OPTiM study. The difference in log(HR)s for the talimogene laherparepvec licensed population and comparator trials ITT population reflect the size of the difference in outcomes due to differences in patient populations. Specifically this reflects the differences in the prognosis of patients between the OPTiM study and the comparator trials.

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

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

The calculated HRs and adjustment factors are presented in Table 15. The adjustment factors adjust the prognosis of patients in the comparator trials to the baseline characteristics patients had in the talimogene laherparepvec licensed

population in the OPTiM trial. The lower the adjustment factor, the bigger the upward survival for the ipilimumab.

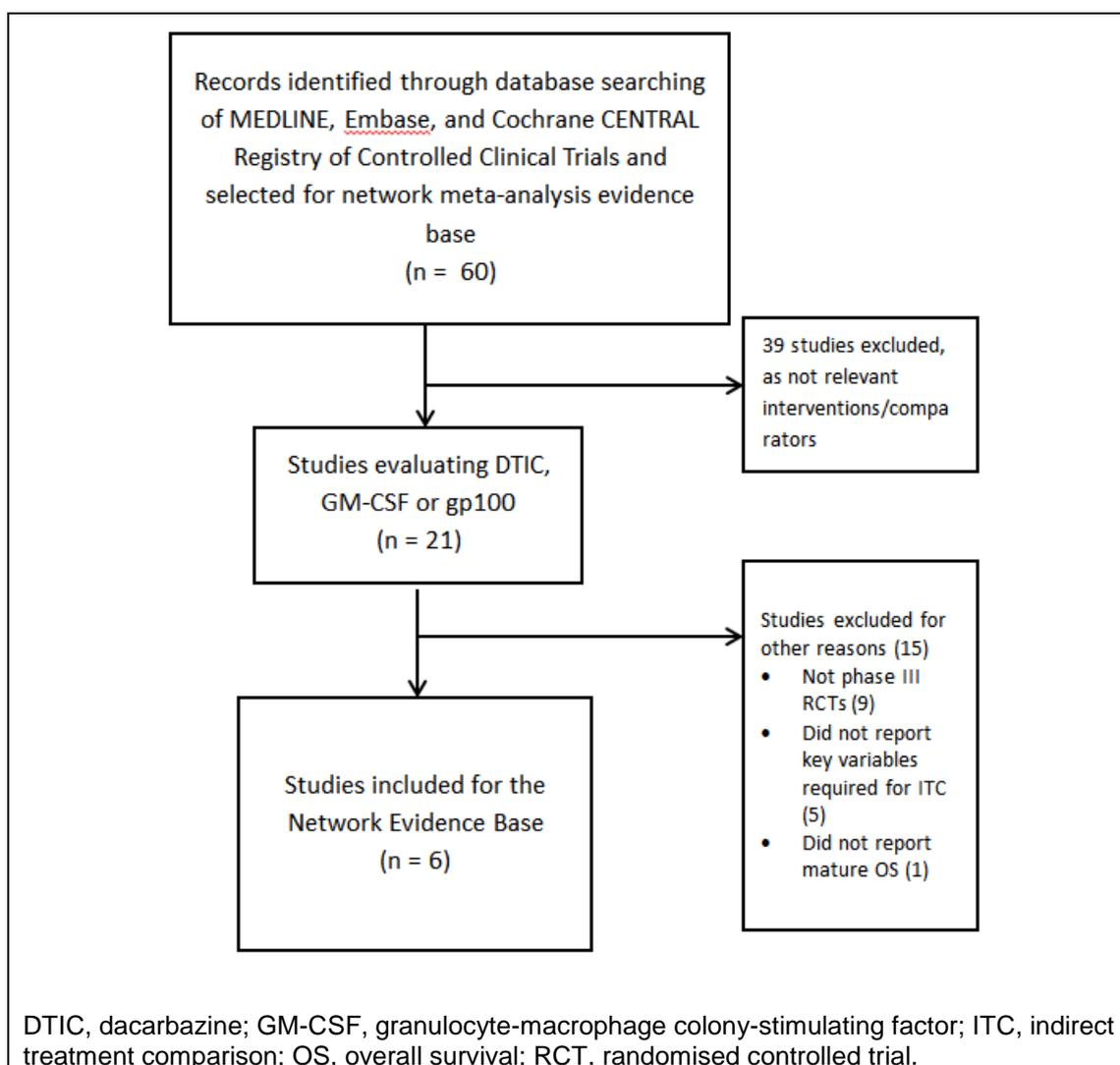
Table 15. Model Coefficients and Adjustment Factors for OS Based on the Modified Korn Model in ITT Population

Treatment	HR equations	Hazard Ratio	Adjustment factor
OS (Based on the Modified Korn Model)			
T-VEC stage IIIB-IVM1c	$\log(\overline{HR}) = -0.154X_{Female=0.41} - 0.400X_{ECOG0=0.71} - 0.285X_{Nonvisceral=0.55} - 0.306X_{Non\ brain\ mets=0.99} - 0.782X_{Normal\ LDH=0.90}$	0.22	NA
Ipilimumab ITT (previously untreated) ^a	$\log(\overline{HR}) = -0.154X_{Female=0.39} - 0.400X_{ECOG0=0.71} - 0.285X_{Nonvisceral=0.17} - 0.306X_{Non\ brain\ mets=0.99} - 0.782X_{Normal\ LDH=0.63}$	0.31	0.72
Ipilimumab ITT (previously treated)	$\log(\overline{HR}) = -0.154X_{Female=0.41} - 0.400X_{ECOG0=0.53} - 0.285X_{Nonvisceral=0.11} - 0.306X_{Non\ brain\ mets=0.891} - 0.782X_{Normal\ LDH=0.61}$	0.35	0.64
^a in the BMS NICE submission for ipilimumab in previously untreated patients, an OS was derived for monotherapy ipilimumab at 3 mg/kg for the previously untreated study population. The adjustment factor calculated in this analysis was applied to the derived OS data. HR, hazard ratio; ITT, intent to treat; NA, not applicable; OS, overall survival.			

9.4 NMA of GM-CSF versus DTIC and gp100: PRISMA flow diagram

The PRISMA flow diagram for RCT evidence for the comparison of GM-CSF with DTIC and gp100 is shown in Figure 13.

Figure 13. PRISMA flow diagram for RCT evidence



9.5 Modified Korn model to compare survival outcomes for GM-CSF versus DTIC and versus gp100

The implementation of the modified Korn adjustment and the consequent results of the adjusted OS are explained in this section. The following steps (which are the same as that done for the comparison of talimogene laherparepvec versus ipilimumab detailed in our company submission) were implemented to calculate the adjusted OS for DTIC and gp100 had they treated a population similar to that of the GM-CSF population in the OPTiM study by stage:

- OPTiM GM-CSF earlier stage disease population (IIIB-IVM1a)
- OPTiM GM-CSF ITT population (stage IIIB-IVM1c)
- OPTiM GM-CSF later stage disease population (IVM1b/c)

Methods

1. The modified Korn model was used to adjust the Kaplan-Meier data for differences between the patient and disease characteristics at baseline using the following five baseline prognostic factors:
 - Gender (female vs. male)
 - ECOG performance status (0 vs. >0)
 - Presence of visceral metastases (No vs. Yes)
 - Presence of brain metastases (No vs. Yes)
 - LDH (Normal vs. Elevated)
2. The adjustment factor to adjust the comparator trial to match GM-CSF patient characteristics was estimated. First, hazard ratios that account for the distributional differences in these five factors were estimated. Each comparator trial's baseline distribution values was substituted into the log(HR) equation for the five baseline prognostic factors taken from modified Korn model (NICE TA319):

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

The same was done for the GM-CSF population in the OPTiM study. The difference in log(HR)s for the GM-CSF population and comparator (DTIC, gp100) trials population reflect the size of the difference in outcomes due to differences in patient populations. Specifically this reflects the differences in the prognosis of patients between the OPTiM study and the comparator (DTIC, gp100) trials.

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

$$HR \left(\frac{GMCSF \text{ baseline characteristics}}{COMPARATOR \text{ baseline characteristics}} \right) = \frac{HR_{GMCSF \text{ baseline characteristics}}}{HR_{COMPARATOR \text{ baseline characteristics}}}$$

The calculated HRs and adjustment factors are presented in Table 16. The adjustment factors adjust the prognosis of patients in the comparator (DTIC, gp100) trials to the baseline characteristics patients had in the GM-CSF population in the OPTiM trial. The lower the adjustment factor, the bigger the upward adjustment in survival for DTIC and gp100.

Table 16. Model Coefficients and Adjustment Factors for OS

Treatment	HR equations	Hazard Ratio	Adjustment Factor
Earlier stage disease population (IIIB-IVM1a)			
GM-CSF	$\log(\widehat{HR}) =$ $-0.154X_{Female=0.45} - 0.400X_{ECOG0=0.63} - 0.285X_{Nonvisceral=1.00} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.97}$	0.20	NA
DTIC ^a	$1.\log(\widehat{HR}) =$ $-0.154X_{Female=0.41} - 0.400X_{ECOG0=0.71} - 0.285X_{Nonvisceral=0.20} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.56}$	0.32	0.64
	$2.\log(\widehat{HR}) =$ $-0.154X_{Female=0.46} - 0.400X_{ECOG0=0.68} - 0.285X_{Nonvisceral=0.16} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.58}$	0.32	0.64
	$3.\log(\widehat{HR}) =$ $-0.154X_{Female=0.41} - 0.400X_{ECOG0=0.70} - 0.285X_{Nonvisceral=0.18} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.68}$	0.29	0.70
	$4.\log(\widehat{HR}) =$ $-0.154X_{Female=0.40} - 0.400X_{ECOG0=0.79} - 0.285X_{Nonvisceral=0.09} - 0.306X_{Non\ brain\ mets=0.94} -$ $0.782X_{Normal\ LDH=0.33}$	0.39	0.52
gp100	$\log(\widehat{HR}) =$ $-0.154X_{Female=0.46} - 0.400X_{ECOG0=0.52} - 0.285X_{Nonvisceral=0.11} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.60}$	0.34	0.60

Treatment	HR equations	Hazard Ratio	Adjustment Factor
ITT population (IIIB-IVM1c)			
GM-CSF	$\log(\widehat{HR}) =$ $-0.154X_{Female=0.45} - 0.400X_{ECOG0=0.69} - 0.285X_{Nonvisceral=0.61} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.88}$	0.22	NA
DTIC ^a	$1.\log(\widehat{HR}) =$ $-0.154X_{Female=0.41} - 0.400X_{ECOG0=0.71} - 0.285X_{Nonvisceral=0.20} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.56}$	0.32	0.69
	$2.\log(\widehat{HR}) =$ $-0.154X_{Female=0.46} - 0.400X_{ECOG0=0.68} - 0.285X_{Nonvisceral=0.16} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.58}$	0.32	0.69
	$3.\log(\widehat{HR}) =$ $-0.154X_{Female=0.41} - 0.400X_{ECOG0=0.70} - 0.285X_{Nonvisceral=0.18} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.68}$	0.29	0.76
	$4.\log(\widehat{HR}) =$ $-0.154X_{Female=0.40} - 0.400X_{ECOG0=0.79} - 0.285X_{Nonvisceral=0.09} - 0.306X_{Non\ brain\ mets=0.94} -$ $0.782X_{Normal\ LDH=0.33}$	0.39	0.57
gp100	$\log(\widehat{HR}) =$ $-0.154X_{Female=0.46} - 0.400X_{ECOG0=0.52} - 0.285X_{Nonvisceral=0.11} - 0.306X_{Non\ brain\ mets=1.00} -$ $0.782X_{Normal\ LDH=0.60}$	0.34	0.65

Treatment	HR equations	Hazard Ratio	Adjustment Factor
Later stage disease population (IVM1b/c)			
GM-CSF	$\log(\widehat{HR}) = -0.154X_{Female=0.45} - 0.400X_{ECOG0=0.78} - 0.285X_{Nonvisceral=0} - 0.306X_{Non\ brain\ mets=1.00} - 0.782X_{Normal\ LDH=0.89}$	0.25	NA
DTIC ^a	$1.\log(\widehat{HR}) = -0.154X_{Female=0.41} - 0.400X_{ECOG0=0.71} - 0.285X_{Nonvisceral=0.20} - 0.306X_{Non\ brain\ mets=1.00} - 0.782X_{Normal\ LDH=0.56}$	0.32	0.79
	$2.\log(\widehat{HR}) = -0.154X_{Female=0.46} - 0.400X_{ECOG0=0.68} - 0.285X_{Nonvisceral=0.16} - 0.306X_{Non\ brain\ mets=1.00} - 0.782X_{Normal\ LDH=0.58}$	0.32	0.79
	$3.\log(\widehat{HR}) = -0.154X_{Female=0.41} - 0.400X_{ECOG0=0.70} - 0.285X_{Nonvisceral=0.18} - 0.306X_{Non\ brain\ mets=1.00} - 0.782X_{Normal\ LDH=0.68}$	0.29	0.86
	$4.\log(\widehat{HR}) = -0.154X_{Female=0.40} - 0.400X_{ECOG0=0.79} - 0.285X_{Nonvisceral=0.09} - 0.306X_{Non\ brain\ mets=0.94} - 0.782X_{Normal\ LDH=0.33}$	0.39	0.65
gp100	$\log(\widehat{HR}) = -0.154X_{Female=0.46} - 0.400X_{ECOG0=0.52} - 0.285X_{Nonvisceral=0.11} - 0.306X_{Non\ brain\ mets=1.00} - 0.782X_{Normal\ LDH=0.60}$	0.34	0.74

Treatment	HR equations	Hazard Ratio	Adjustment Factor
<p>^a 1. DTIC in ipi previously untreated trial (Robert et al, 2011). 2. DTIC in vemurafenib trial (McArthur et al, 2014)). 3. DTIC in dabrafenib trial (Hauschild et al, 2012). 4. DTIC (Daponte et al, 2013)</p> <p>DTIC, dacarbazine; HR, hazard ratio; ITT, intent to treat; OS, overall survival; GM-CSF, granulocyte-macrophage colony-stimulating factor.</p>			

3. The adjusted OS for DTIC and gp100 was estimated by adjusting their respective Kaplan-Meier curves using the calculated adjustment factor to reflect outcomes in a GM-CSF-like population:

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

4. The uncertainty surrounding the adjustment of OS was characterised by a 95% prediction interval. The standard errors provided in TA319 for the modified Korn equation were used to generate the 95% CI for the HR. The adjusted mean OS (95% CI) is 19.0 (18.2, 19.8) for DTIC and 14.3 (13.3, 15.6).
5. Where multiple curves were available for the same comparator, they were pooled by the modified Mantel-Haenszel method.

9.6 Comparison of GM-CSF versus DTIC and gp100 using original Korn model

Figure 14 and Figure 15 compare OS for GM-CSF versus DTC and gp100 using the original Korn model (Korn et al, 2008).

Figure 14. OS comparison of GM-CSF versus DTIC (Original Korn)

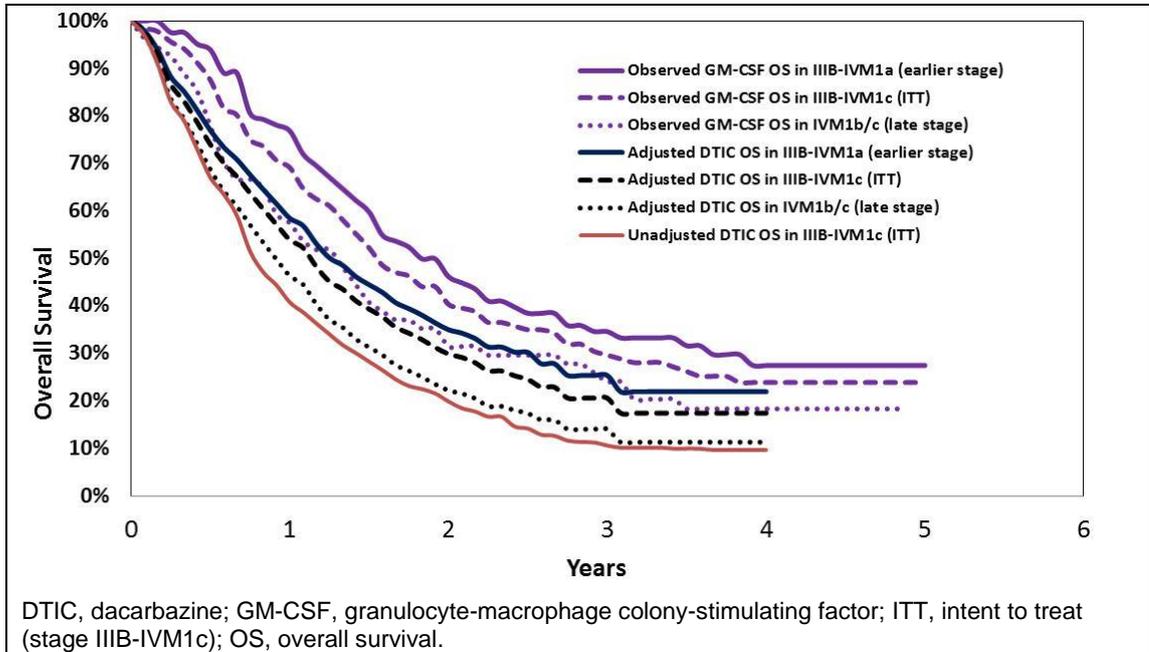
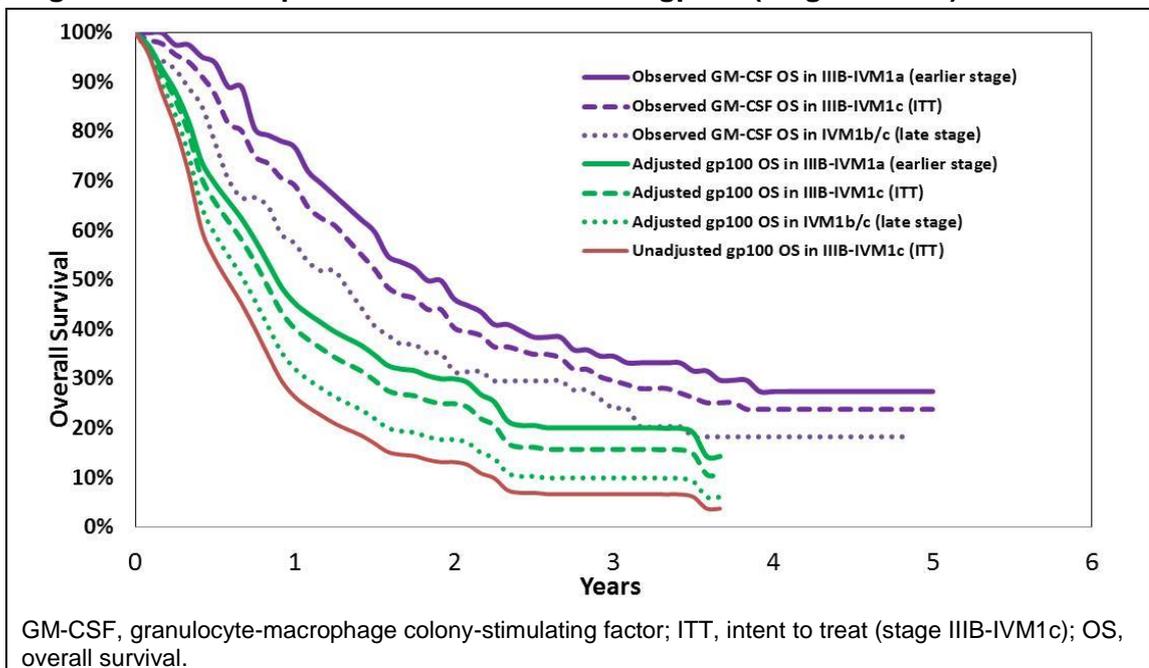


Figure 15. OS comparison of GM-CSF versus gp100 (Original Korn)



9.7 ITC of talimogene laherparepvec versus ipilimumab: sensitivity analyses

To explore the robustness of the primary ITC of talimogene laherparepvec versus ipilimumab in earlier stage disease, a number of sensitivity analyses have been conducted. These are summarised below.

Weighting ipilimumab data by line of therapy

The main ITC analysis assumed that ipilimumab efficacy does not differ by line of therapy as previously accepted by NICE (NICE TA319, 2014). However, the ACD raised concerns around combining ipilimumab first and second-line data noting that this assumes that survival patterns are equivalent regardless of line of therapy (ACD section 3.27). We therefore conducted a sensitivity analysis where the ipilimumab data was weighted by line of therapy proportional to that observed in the talimogene laherparepvec OPTiM licensed population (55% first-line; 45% second line). This analysis gave similar results to the main ITC of talimogene laherparepvec versus ipilimumab: HR (95% CI) 0.87 (0.52, 1.44), P=0.59.

Adjustment to data used from ipilimumab previously treated RCT (MDX010-20)

The main ITC used the OS HR for ipilimumab versus gp100 in patients with stage M0, M1a and M1b disease (0.47) to represent the effect of ipilimumab in previously treated patients with earlier stage disease since no data were available for stage M0-M1a only. We therefore conducted a sensitivity analysis to estimate the effect of ipilimumab in stage M0-M1a patients only by using the ITT HR (0.64) to represent the M1b patients. The estimated number of events and OS HR in previously treated stage M0-M1a patients was then calculated: HR (95% CI) 0.13 (0.04, 0.47).

As described previously (section 3.2), a weighted average of the OS treatment effect estimates for previously untreated and previously treated M0-M1a patients was then calculated. This resulted in a pooled HR (95% CI) of 0.65 (0.41, 1.03) for ipilimumab versus DTIC or gp100 in earlier stage disease.

Using this revised data led to similar results to the main ITC of talimogene laherparepvec versus ipilimumab: HR (95% CI) 0.87 (0.49, 1.54), P=0.63

9.8 Cost effectiveness acceptability curves for talimogene laherparepvec versus DTIC and BSC

Figure 16 shows the cost effectiveness acceptability curve for talimogene laherparepvec versus DTIC (GM-CSF costed as DTIC). The probability of being cost effective at the £20k threshold and at the £30k threshold is 9.0% and 87.1%, respectively.

Figure 16. Cost effectiveness acceptability curve for talimogene laherparepvec versus DTIC (GM-CSF costed as DTIC), PAS price for talimogene laherparepvec

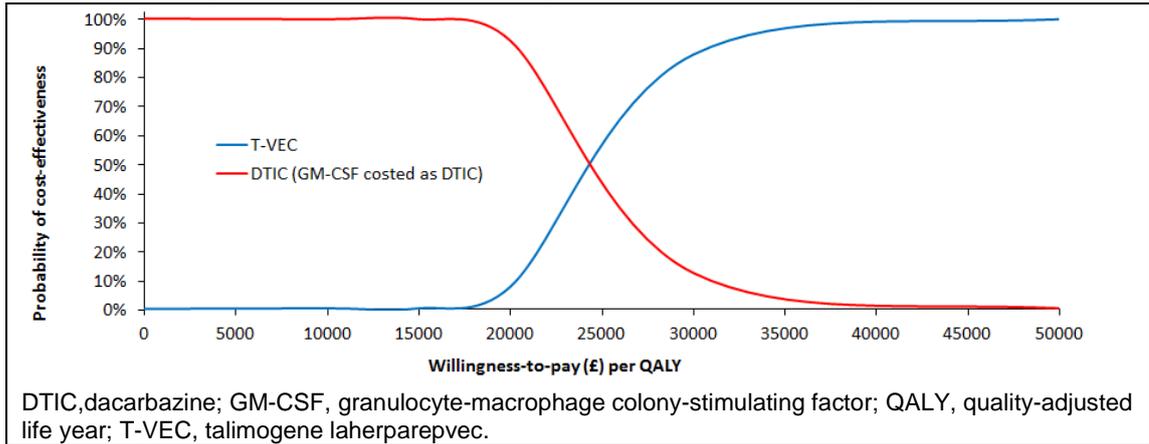
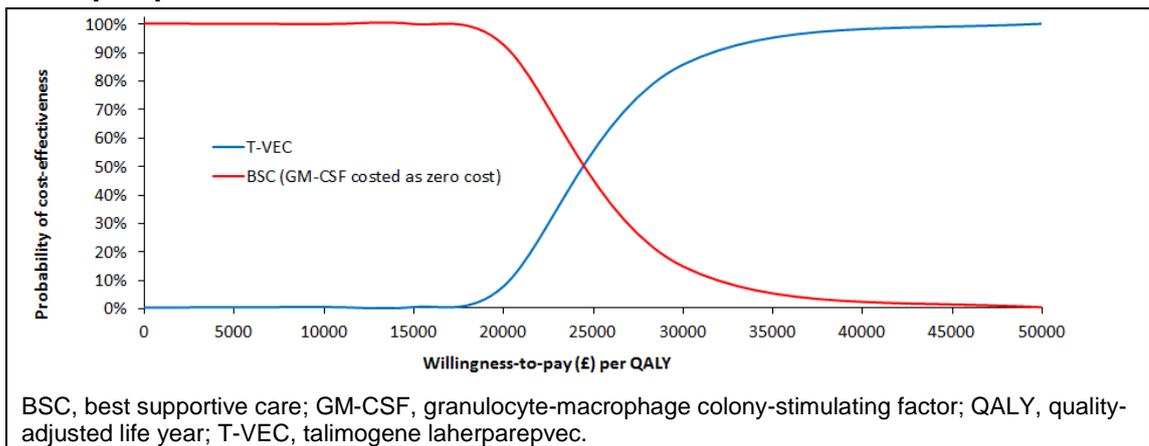


Figure 17 shows the cost effectiveness acceptability curve for talimogene laherparepvec versus BSC (GM-CSF costed as zero cost). In the talimogene laherparepvec versus BSC model, the probability of being cost effective at the £20k threshold and at the £30k threshold is 7.1% and 85.7%, respectively.

Figure 17. Cost effectiveness acceptability curve for talimogene laherparepvec versus BSC (GM-CSF costed as zero cost), PAS price for talimogene laherparepvec



Appraisal consultation document:

The Appraisal Consultation Document accurately summarises the advances made in the treatment of metastatic melanoma in the last five years. The UK is in the privileged position of having many of these treatments available for patients. However, despite a significant improvement in the median survival for patients, from 9 months to approximately 30 months, the majority of patients with advanced disease still die of melanoma. Additionally, there are groups of patients with a high risk of toxicity from existing strategies (ipilimumab or pembrolizumab) because of pre-existing autoimmune conditions, for whom ipilimumab and pembrolizumab are not suitable. Further treatment options and newer treatment strategies are urgently required.

Oncolytic therapy such as talimogene laherparepvec (T-VEC) is one such approach for patients with locally advanced (inoperable stage 3), or stage 4 M1a disease. The ACD correctly summarised the outcome of the OPTIM study, noting the challenges provided by the use of a non-standard trial endpoint and study comparator. Nevertheless, the OPTIM study identified a subgroup of patients with durable responses and this led to the approval of T-VEC by the FDA and EMA.

T-VEC is a first-in-class agent with a novel dual action. A major advantage is the low risk of significant toxicity and the potential for systemic benefit from a local therapy, in contrast to existing immune therapies. Approximately 10%-15% of patients have troublesome locally advanced or 3c/M1a disease. Whilst these patients are likely to benefit from the current NICE-approved agents, they are also the group of patients who will benefit from T-VEC. Increasing treatment options for patients (ie targeted therapy and immunotherapy) have already been shown to improve survival in advanced melanoma, so it is logical to further expand new treatment options for eligible patients.

A major challenge for the NICE Appraisal of T-VEC was the lack of a standard comparator; the comparator used in the OpTIM trial is clinically considered inactive. Although Ipilimumab was approved

as a standard comparator, in retrospect either an anti-P1 antibody, targeted therapy or electrochemotherapy would have been more appropriate. Compared to ipilimumab, T-VEC stands up well in terms of efficacy, durable benefit and, importantly, very low risk of toxicity. For many eligible patients, T-VEC would be given in preference to other licensed and approved treatments. Review in clinical practice at Southampton since the previous committee meeting has identified three patients in the intervening weeks who would be excellent candidates for T-VEC treatment as they fit the EMEA treatment criteria but were not suitable for immunotherapy due to previous toxicity or pre-existing autoimmune disease. These patients will lose out if they cannot be offered T-VEC.

The next major advance in the treatment of melanoma will be combination immunotherapy. Early studies combining T-VEC with ipilimumab, and T-VEC with anti-PD1 antibodies, have shown significant activity in converting non-responding patients to become responders. This has a huge implication not just for melanoma but for many other cancers including sarcoma, head-and-neck cancer and breast cancer. Whilst not directly pertinent to the NICE decision, there is a risk that if patients cannot access T-VEC within the licensed indication, this may impact on future developments in combination.

In summary, T-VEC is an appropriate treatment for a small subgroup of patients. It is an effective treatment with substantially less risk of significant toxicity compared to ipilimumab, and with advantages over the other potential treatment options not considered in the NICE Appraisal. Talimogene laherparepvec would be the treatment of choice for a limited number of patients.

Submission online.

NICE Melanoma (metastatic) - talimogene laherparepvec [ID508]
NICE in development GID TAG509

Appraisal consultation document:

The Appraisal Consultation Document accurately summarizes the advances made in the treatment of metastatic melanoma in the last five years. The UK is in the privileged position of having many of these treatments available for patients. However, despite a significant improvement in the median survival for patients, from 9 months to approximately 30 months, the majority of patients with advanced disease still die of melanoma. Additionally, there are groups of patients with high risk of toxicity from existing strategies (ipilimumab or pembrolizumab) because of pre-existing autoimmune conditions or previous toxicity, for whom ipilimumab and pembrolizumab are not suitable. Further treatment options and newer treatment strategies are urgently required.

Oncolytic therapy such as talimogene laherparepvec (TVEC) is one such approach for patients with locally advanced (inoperable stage 3), or stage 4 M1a disease. The ACD correctly summarised the outcome of the OPTIM study, noting the challenges provided by the use of a non-standard trial endpoint and study comparator. Nevertheless, the OPTIM study identified a subgroup of patients with durable responses, and this led to the approval of TVEC by the FDA and EMA.

TVEC is a first-in-class agent with a novel dual action. A major advantage is the low risk of significant toxicity and the potential for systemic benefit from a local therapy, in contrast to existing immune therapies.

Approximately 10-15% of patients have troublesome locally advanced or 3c/M1a disease. Whilst these patients are likely to benefit from the current NICE-approved agents, they are also the group of patients who will benefit from TVEC. Increasing treatment options for patients (ie targeted therapy and

immunotherapy) have already been shown to improve survival in advanced melanoma, so it is logical to further expand new treatment options for eligible patients.

A major challenge for the NICE Appraisal of TVEC was the lack of a standard comparator; the comparator used in the OpTIM trial is clinically inactive, ie was a placebo. Although Ipilimumab was approved as a standard comparator, in retrospect either an anti-P1 antibody, targeted therapy or electrochemotherapy would have been more appropriate. Compared to ipilimumab, TVEC stands up well in terms of efficacy, durable benefit and, importantly, very low risk of toxicity. For many eligible patients, TVEC would be given in preference to other licensed and approved treatments.

Review in our own clinical practice (Southampton) since the previous committee meeting has identified three patients presenting in the intervening weeks, who would be excellent candidates for T-VEC treatment as they fit the EMEA treatment criteria but were not suitable for immunotherapy due to previous toxicity or pre-existing autoimmune disease. These patients will lose out if they cannot be offered T-VEC.

The next major advance in the treatment of melanoma will be combination immunotherapy. Early studies combining TVEC with ipilimumab, and TVEC with anti-PD1 antibodies, have shown significant activity in converting non-responding patients to become responders. This has a huge implication not just for melanoma but for many other cancers including sarcoma, head-and-neck cancer and breast cancer. Whilst not directly pertinent to the NICE decision, there is risk that if patients cannot access TVEC within the licensed indication, this may impact on future developments in combination.

In summary, TVEC is an appropriate treatment for a small subgroup of patients. It is an effective treatment with substantially less risk of significant toxicity compared to ipilimumab, and with advantages over the other potential treatment options not considered in the NICE Appraisal. Talimogene laherparepvec would be the treatment of choice for a limited number of patients.

Comments on the ACD Received from the Public through the NICE Website

Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
██████ ██████	NHS Professional		<p>I am a medical oncologist working at Guy's and St Thomas NHS Foundation Trust treating malignant melanoma. I am the lead for skin cancer research in the Trust and a clinical academic involved in solid tumour T-cell immunotherapy research. I am the local principle investigator on a phase 2 study of talimogene laherparevec in melanoma. We have treated the largest group of patients on this trial to date.</p> <p>Having read the appraisal consultation document it is clear that there is difficulty in deciding on the first in class advanced therapy medicinal product (ATMP) talimogene laherparepvec's efficacy based on the patient population covered by the license. The majority of patients treated with the NICE scope comparator Ipilimumab with unresectable stage IIIB-IVM1a was low. In practice these patients are managed depending on the distribution of their disease. Modalities such as ECT and isolated limb perfusion (for which reliable randomised data supporting efficacy does not exist) are used but, in this new era of systemic immunotherapy, we are moving to treat with checkpoint inhibition. So, in clinical practice, the majority of patient with unresectable stage IIIB-IVM1a melanoma will receive CTLA4 or PD1 directed immunotherapy. These agents come with the risk of systemic autoimmune toxicities which can, on occasion, be severe for patients. In this patient population, where therapy is needed and evidence is thin on the ground, data from the 57% of patients on the OPTiM trial with stage IIIB-IVM1a disease offers solid randomised evidence that there is now an effective therapy. In my view the lack of a clear cross comparator from other systemic therapy trials only serves to highlight the importance of this exciting ATMP for a group of patients who have long been in need of effective therapy.</p> <p>Our experience with talimogene laherparepvec is, for well selected patients with accessible and injectable disease, the drug represents an excellent, innovative and very well tolerated alternative to both therapies such as ECT and limb perfusion and systemic immunotherapy. The treatment causes minimal and manageable side effects and can be given in clinic avoiding the need for chair space on our busy cancer day unit.</p> <p>Treating unresectable melanoma is a rapidly evolving field. The paradigm shift from cytotoxic agents to targeted therapy and immunotherapy over the past 5 years has dramatically changed the landscape of survival for patients. Having talimogene laherparepvec as one of the options for patients in the NHS is key to ensuring we are</p>	██████████ ██████████	England	No	

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			offering the best possible therapy for our patients - allowing innovation to impact on outcomes.				
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Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
	NHS Professional		<p>I am a clinician scientist specializing clinically in melanoma, and in translational immunotherapy in my research. I have recently moved to the Institute of Cancer Research in London, and my specific interest is in oncolytic immunovirotherapy. I have published extensively in this field, across the research spectrum, from pre-clinical studies to early clinical trials (including biological endpoint translational studies). My opinion is that TVEC is an Advanced Therapeutic Medicinal Product, and represents genuine innovation in the treatment of melanoma. In my experience having taken part in TVEC trials and administered the virus to patients, TVEC is in general well tolerated compared to many existing therapies (eg ipilimumab), and acceptable to patients, and would be a useful treatment option for the small number of patients with injectable stage IIIB/C/IVM1a disease.</p> <p>TVEC, if it behaves as do other immunotherapies (which is what I would expect as the data matures), offers the hope, even as a single agent, for inducing prolonged periods of remission in this small group of appropriate patients.</p> <p>Importantly other treatments which may currently be prescribed for patients with Stage IIIB/C/IVM1a disease (including BRAF inhibitors as well as checkpoint inhibitor</p>	Prof of Translational Immunotherapy	England	No	N/A

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Date: 13th April 2016

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			<p>antibodies), all have the potential for associated significant, and sometimes severe, side effects which may make their use less desirable in patients with low volume, slowly progressing metastatic disease, for whom TVEC would be an alternative, earlier treatment.</p> <p>It is worth noting that TVEC is effective in treating melanoma regardless of BRAF status. For patients with relatively low volume, good prognosis metastatic disease it is becoming increasingly attractive to treat BRAF mutant patients with an immunotherapy first, reserving BRAF inhibitors for later therapy; indeed, this is an approach increasingly being requested by patients themselves in the clinic. This is understandable and appropriate, given the increasing evidence that immunotherapies offer the potential for sustained benefit, as illustrated by the long-term survival figures of around 20% in patients given CTLA4 blockade.</p> <p>Although BRAF inhibitors have a higher response rate than immunotherapies, no such long-term “tail” on the survival curve is seen. It is my opinion that the same long-term remissions are likely to be seen in due course in a proportion of patients treated with intratumoural T-Vec, regardless of BRAF status (even beyond the 5 years follow up we currently have data for)</p> <p>The treatment scheduling of treatment in metastatic melanoma is evolving rapidly, and now needs to balance not only the standard readouts of toxicity and efficacy, but the newer paradigms of potential long-term remission (even cure), and keeping treatment options “in reserve” (be they small molecule or immunotherapy), to allow the use of optimal sequential therapies for long-term management of what is fortunately becoming more of a chronic disease, than a short-term, dismal prognosis cancer. T-Vec significantly adds to the options within this increasingly complex management challenge for clinicians treating metastatic melanoma.</p> <p>The consequence of TVEC not being approved by NICE is that there will be a set of patients, albeit relatively small, with limited metastatic stage IIIB/C/IV M1a disease denied access to an efficacious, well tolerated treatment potentially able to induce long-term remissions. These patients will instead have to be treated earlier with more toxic small molecule/immunotherapy agents (which cannot then be kept in reserve), which, in fact, have a relatively limited evidence base in this particular group of melanoma patients.</p>				
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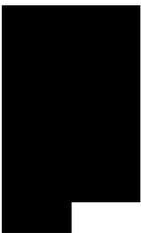
Comments on the ACD Received from the Public through the NICE Website

Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
[REDACTED]	CEO - Patient organisation	[REDACTED]	Melanoma patients are extremely disappointed in the decision. TVEC offers an important, novel, additional option in this small cohort of patients. NICE's position is that TVEC should not be recommended because there is a lack of data for TVEC's comparator treatments if they are being used in the earlier stage disease where TVEC is positioned. NICE themselves acknowledge that TVEC has an improved tolerability profile than later lines of treatment. Patients and clinicians need to have access to as many innovative treatments as possible.	CEO	England	No	

Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
[REDACTED]	NHS Professional		<p>NICE appraisal of T Vec for the treatment of malignant melanoma has failed to take into consideration the potential value of a treatment that has a unique mechanism of action, and which is the most convincing evidence of a successful therapeutic cancer vaccine ever published. I feel strongly that T vec should be made available for suitable patients with malignant melanoma and provide a routine treatment option for defined specific patients. Although immunotherapy such as Provenge in prostate cancer have been associated with improved survival, only T Vec has provided clear radiological evidence of abscopal tumour regression and improved disease control. The committee stated that a new agent with a novel mechanism of action and improved tolerability would be valuable for patients with stage IIIB/c IV M1a melanoma, if it could be shown to be as clinically effective as other immunotherapy agents (in this case ipilimumab (Ipi)).</p> <p>This is a flawed argument in that:</p> <ol style="list-style-type: none"> 1. T Vec cannot be regarded to be a direct comparator with ipi in terms of their biology, patient stage and selection, mode of action and especially in view of the massively contrasting toxicity profiles. 2. T-vec creates a new treatment option wholly unrelated to ipi or other drugs, 				

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			<p>and this is its value rather than its limitation</p> <p>3. There is clear and defined unmet need in these stages of an inevitably aggressive malignancy, despite the availability of ipi.</p> <p>4. There are enormous quality of life benefit for T vec over immune checkpoint inhibitors, and no life threatening toxicities</p> <p>5. Not having T vec as a treatment option either gives patients no treatment option or forces premature use of toxic and expensive drugs such as ipi, and downstream reduces options for treatment if disease progresses. At this point the patient may not be fit enough for ipi.</p> <p>6. Ipi therapy is associated with hospitalisation and fatalities, even now in an era of routine use and considerable experience by specialist in large centres. T vec has never shown a comparable adverse toxicity profile.</p> <p>7. The numbers of patients suitable for T vec nationally per annum are modest</p> <p>8. Patient choice has to be respected and an integral component of optimal disease management</p>				
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Author name	Role	Organisation	Comment	Job Title	Location	Declared Interest	Disclosure
	NHS Professional		<p>The optimum management of non-resectable stage III/IVA melanoma remains unclear, with few options having been specifically studied in this setting. T-VEC is an exception, with the phase III OPTIM study having included a well defined and large cohort of patients in this setting. The efficacy and toxicity were both very favourable, demonstrating that T-VEC provides a valuable option in this setting. Indeed, the panel agreed that “the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for patients with metastatic melanoma.</p> <p>The submission sought to compare T-VEC principally with ipilimumab, following a previous scoping exercise. There have been no direct comparisons between T-VEC and ipilimumab, and as such any comparisons were indirect. In addition the activity of</p>		England	Yes	

Comments on the ACD Received from the Public through the NICE Website

			<p>ipilimumab in this setting is not fully known, as few patients with this stage disease were included in large phase trials. Thus, the difficulty in comparing the two agents was predominantly due to a lack of data for ipilimumab in this setting, rather than for T-VEC.</p> <p>The modelling in the submission included an adjustment to ipilimumab's efficacy in this setting. The need for such an adjustment is based at least partly on the assumption that lower volume disease may respond more favourably compared to higher volume later stage disease. One way of at least partly addressing this would be to compare with the efficacy of ipilimumab in the adjuvant setting where residual disease is at a minimum. In a recent large adjuvant study of ipilimumab (i.e. resected stage III disease), the 3-year recurrence-free survival was 46.5% in those treated with ipilimumab and 34.8% in the placebo arm (1). This implies that recurrence rate was reduced from 65.2% to 53.5%, i.e. by 11.7%. In other words recurrences were "prevented" in about 18% of those at risk, a similar degree of clinical efficacy to that seen in advanced disease, where approximately 20% of patients gain benefit (respond to treatment or have prolonged stable disease). OS data has not yet been reported.</p> <p>Notably, in the adjuvant study the 2-year relapse free rate was 51.5% (ipilimumab) compared to approximately 40% for patients with Stage III/IVA disease receiving T-VEC in OPTIM. Considering the worse prognosis of patients in the latter group, it would appear unlikely that ipilimumab could be significantly more active in T-VEC in the unresectable stage III/IVA groups.</p>				
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Ladies and Gentlemen of NICE,

I applaud your decision to reject Amgen's T-vec !

All of these new Immuno-therapy drugs should be called immune suppression treatments. To use therapy is misleading.

My personal experience will hopefully provide you with an up close and truly personal look at what happens after taking these drugs. I've had Keytruda (two infusions). Since my Oncologist didn't see any beneficial reduction in the right axillary adenopathy (swollen lymph node) he decided to use Tafinlar and Mekinist because I had the braf mutation. Then he decided to use Opdivo and Yervoy together. From all of these treatments, I experienced a profound level of physical debilitation. One week after the Opdivo/Yervoy infusion, I broke out in a rash so severe that I made a formal complaint to the FDA via their Medwatch program.

When I first started this excruciating journey, I was diagnosed with metastatic melanoma. When this happens, one seeks the assumed professional advice of a Oncologist. I asked him at the beginning, "What would you need to see that would provide you with evidence that the treatment is working" ? He said the only way was if the mass or tumor

under went reduction in size. None of the treatments reduced the tumor!

When I started the treatments I stopped taking a composition called GBF. It was developed by a retired pharmaceutical chemist that had a significant level on knowledge on both nutrition and biochemistry. GBF is able to elevate glutathione in one's body. I stopped taking it so as to allow the treatments to have their desired effect.

When the treatments didn't provide any reduction in the tumor, but one hell of a lot of physical debilitating problems, I went back on GBF. However, this time I included Selenium which then produces glutathione peroxidase. What happened then was quite interesting. The profound side effects started to dissipate. Most interesting was the mass also started to undergo reduction in size ! I did a search on PUBMED and found this study: <http://www.ncbi.nlm.nih.gov/pubmed/10503874>

It appears from this study that glutathione + Selenium = glutathione peroxidase (GPX)

may be a potential prevention and intervention for melanoma and just maybe other cancers.

I've contacted Fred Hutchison Cancer Research Institute to see if we might be able to conduct a pilot study.

Incidentally, NO SIDE EFFECTS with GPX.

Response to TVEC NICE ACD

I am writing to express my grave disappointment at the recent result issued by the NICE Appraisal Committee that heard evidence on T-VEC. If this result is ratified, it will result in this novel technology being unavailable to patients in the NHS. I believe that there are grounds to ask the committee to reconsider its position.

It appears that the main reason for ruling against T-VEC was based on an unwillingness to accept the indirect comparison of T-VEC with Ipilimumab (despite the fact that this was the remit under which the evaluation was conducted). This matter relates largely to the fact that there is no directly comparable dataset to provide data on the activity of Ipilimumab in the population that is the target group for T-VEC. This judgement was made despite efforts to provide a modelled dataset based on Korn (and modified Korn) methodology. I believe that there are grounds to re-visit this issue and to contest the assertion of the reviewers that there is a risk that T-VEC may, in fact, be significantly inferior to T-VEC. Having said that, in the absence of a head-to-head trial of T-VEC vs Ipi (or another immunotherapy) modelled data such as those that were presented represent the only possible way of setting a new technology like T-VEC in context in a population of melanoma patients with stage IIIB/IIIC/IVM1a disease. If modelled data are not used as a basis of comparison, I am very concerned that there is no way in which to assess T-VEC fairly and to give patients the prospect of receiving this therapy. As a specialist who treats patients with melanoma – including patients who meet the European indications for its use – I am alarmed that this treatment may be denied to patients who, in my opinion, stand a very high chance of deriving clinical benefit.

The importance of treatment-related toxicities has been discussed but, in my opinion, the very low toxicity burden of T-VEC may not have been given appropriate consideration. T-VEC is markedly different from existing, licensed immunotherapies and may represent a very favourable treatment option for specific patient groups. Again, I hope that matter is considered once more.

The committee noted the novelty of the therapy – but this did not sway the overall decision. Again, I believe that there are grounds to revisit this matter and to consider T-VEC as a unique technology that has the potential to change the way in which melanoma is treated.

Overall, I would hope that there is an opportunity to appeal this initial ruling and to have a chance to make this treatment available for patients who stand to derive very significant benefits.

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Talimogene laherparepvec for treating metastatic melanoma Addendum [ID508]: ERG consideration of issues raised in the Amgen 'Response to appraisal consultation document (dated 13 April 2016)'

Confidential until
published

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CONTAINS COMMERCIAL IN CONFIDENCE DATA



Talimogene laherparepvec for treating metastatic melanoma [ID508]

Addendum: ERG consideration of issues raised in the Amgen 'Response to appraisal consultation document (dated 13 April 2016)'

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1 INTRODUCTION

Following the issuing of the appraisal consultation document (ACD) for talimogene laherparepvec (T-VEC) for treating metastatic melanoma by NICE,¹ the company responded with a 55 page document and new model which raised a number of concerns with the critique and interpretation of evidence presented in its original submission² and model. In doing so, the company made five key arguments:

1. The Korn methods, used to evaluate comparative effectiveness in earlier stage disease, are suitable to adjust ipilimumab survival data to the earlier stage population. They are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show T-VEC is at least as effective as ipilimumab in the worst-case scenario.
2. Analyses using Korn methods to evaluate comparative efficacy in the broader population of patients including later stage disease, support the case that T-VEC is at least as effective as ipilimumab.
3. Analysis using conventional indirect treatment comparison (ITC) methods to compare T-VEC with ipilimumab in earlier stage disease also shows that T-VEC is at least as effective as ipilimumab; supporting the findings using Korn methods, and providing external validity.
4. Cost effectiveness analysis show that T-VEC is cost effective versus ipilimumab even when using the ERG method for OS extrapolation; provided that it is consistently applied to both treatments.
5. There is robust evidence of clinical and cost effectiveness of T-VEC versus recognised treatments (dacarbazine [DTIC]) and best supportive care (BSC) but with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that T-VEC is cost effective versus ipilimumab.

In addition, the company noted that the NICE Appraisal Committee had raised concerns around the post-hoc nature of the OPTiM subgroup analysis in patients with non-visceral disease and so presented a response to this. Finally, the company highlighted factual inaccuracies within the ACD.¹

NICE asked the ERG to present a review of the company's response to the ACD.¹ This document presents the findings from the ERG's review of its five main arguments and the post-hoc nature of the OPTiM subgroup analysis.

2 GENERATING A SYNTHETIC IPILIMUMAB COMPARATOR

The company response to the ACD¹ issued for the appraisal of talimogene laherparepvec (T-VEC) for treating metastatic melanoma includes consideration of a number of issues, but initially concentrates on the company's attempts to generate a comparator arm using hazard ratio adjustments to trial data from two published ipilimumab studies (MDX010-20³ and CA184-024,⁴) which previously featured in NICE appraisals of treatments for melanoma (TA268⁵ and TA319⁶).

Central to this strategy is the company's use of an algorithm referred to as the 'modified Korn model' which the company prefers to the [original] 'Korn model'. The use of this terminology may in fact be misleading.

The original Korn model was fully described in the Journal of Clinical Oncology 2008⁷ and relates to an exercise based on the analysis of individual patient data from 2,100 patients in 42 trials (70 arms) of different potential melanoma therapies which were later deemed to be ineffective. The authors sought to identify patient characteristics that were influential on patient outcomes (overall survival [OS] and progression-free survival [PFS]). The objective was therefore to provide a 'natural history' foundation for triallists to aid in the design of future trials of candidate melanoma treatments. The analysis was carried out using proportional hazard (PH) modelling.

The origin of the alternative 'modified Korn model' employed by the company is obscure, and the data on which it is based are not described in publicly available sources. The modified model was developed by or on behalf of Bristol-Myers-Squibb (BMS) for their evidence submission to NICE for ipilimumab in previously untreated melanoma patients (TA319)⁶ though no details are available in the public domain. As the only qualitative differences between the structures of the two proportional hazard models are the addition of a variable for elevated lactate dehydrogenase (LDH), and another to refine the representation of performance status, it is possible that the calibration data set remains the same as that originally used by Korn (with the addition of elevated LDH). If so, then the validity of the resulting adjustment equation is restricted to those patients and treatments used for calibration i.e. patients treated with ineffective/placebo/ BSC regimens. This restriction would therefore preclude its use for adjusting patient outcomes when active treatments are being compared, whether as the intervention or the control arm of a clinical trial, since there is no way of assessing the likely interactions between model variables for active treatments.

For the 'modified Korn model' to be valid for adjusting patient outcomes for ipilimumab as an active comparator, the model would need to be calibrated against patient-level data from trials of ipilimumab in similar patient populations, but there is no indication in the company submission (CS) that this is the case. Therefore, there remains uncertainty as to whether adjustment of OS and PFS estimates for ipilimumab-treated patients using the 'modified Korn model' is valid.

There remain three important concerns with the use made by the company of the BMS 'modified Korn' adjustment model:

1. Has the algorithm been correctly applied?
2. Is it appropriate to use the Korn OS model to adjust PFS clinical data?
3. Is the use of a PH model appropriate in this appraisal?

2.1 Calculation of hazard ratios and adjustment factors for overall survival

The BMS Cox PH model ('modified Korn' model) features five patient characteristics that determine the population hazard ratio relative to a baseline survival curve:

- Proportion female (0 to 100%)
- Proportion with ECOG performance status 0 (0 to 100%)
- Proportion without visceral disease (0 to 100%)
- Proportion without brain metastases (0 to 100%)
- Proportion with normal LDH (0 to 100%).

Balch et al 2009⁸ described an important change in the 7th edition of the AJCC staging criteria for melanoma:

“The updated AJCC Melanoma Staging Database demonstrated that an elevated serum LDH is an independent and highly significant predictor of survival outcome among patients with stage IV disease....Therefore, serum LDH should be measured at the time stage IV disease is documented, and if the LDH level is elevated, those patients are assigned to M1c regardless of the site of their distant metastases.”

By this definition the only patients with elevated LDH in the licensed subgroup should be among the group with IIIB and IIIC disease. In the GM-CSF arm of the OPTiM trial⁹ only five patients in total were reported to have elevated LDH (3.9% of those with known LDH status), but the calculations shown by the company in Table 16 of their response to the ACD show 87% of patients in the IIIB/IIIC/M1a subgroup with normal LDH, equivalent to 11 patients with elevated LDH. This discrepancy arises as a result of differences in the denominator used: if patients with unknown LDH status are excluded, then the five patients with elevated LDH constitute 12.1% of the GM-CSF arm population (and 87.9% of patients in the IIIB/IIIC/M1a subgroup with normal LDH). The correct denominator to use also impacts upon, the estimation of the hazard adjustment factor for each of the potential comparators (derived from data reported by MDX010-20³ CA184-024,⁴ BRIM-3,¹⁰ BREAK-3¹¹ and Daponte et al 2013¹²). It raises the possibility that similar discrepancies may have arisen when deriving values for the proportion of patients with normal LDH parameter from the other trials in the evidence network. This adds additional uncertainty to the derivation of hazard ratio adjustment values, and consequently casts doubt on the calibrated synthetic comparator to T-VEC.

2.2 Adjustment of PFS patient outcomes based on OS modified Korn model

The company claims that there is a “high expected correlation between PFS and OS” and uses this as justification for adopting the modified Korn OS model to adjust PFS outcomes. This claim is clearly unsupported. Figure 1 demonstrates that OS and PFS hazards occur at very different times in the gp100 control arm of MDX-010-20.³ This means that the PH assumption (which requires that the trial data should closely follow the dashed line at all time points) is violated.

The company points out that using the original Korn PFS model leads to serious anomalies in which PFS estimates can exceed estimated OS values. This problem cannot be considered a sufficient justification for wrongly applying the OS modified Korn model to both OS and PFS. Instead, it is a clear indication that the whole approach adopted by the company to generate a synthetic ipilimumab comparator is fundamentally unsound.

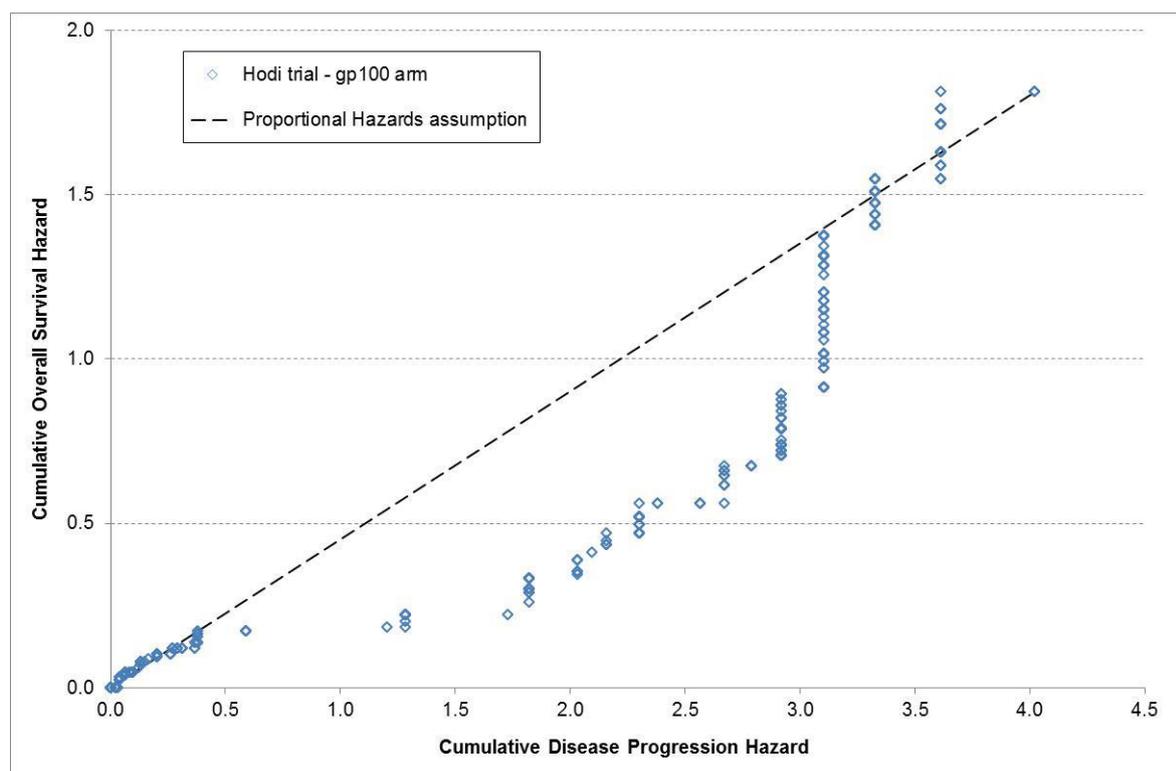


Figure 1 Test of the validity of the proportional hazards assumption between PFS and OS cumulative hazards in the gp100 control arm of MDX010-020 (Trial observations should lie close to the PH line if PFS and OS events follow similar temporal trends)

2.3 Validity of proportional hazard model results for overall survival estimation

The company relies on the results of an ITC to support the claim that T-VEC provides superior survival outcomes compared with ipilimumab (Section 3 of the company ACD response document). The comparison between T-VEC and ipilimumab incorporated into the company's decision model depends upon the integrity of the ITC represented in Figure 6 of the company's response to the ACD. This links the OPTiM trial⁹ (T-VEC vs GM-CSF) to ipilimumab through two ipilimumab clinical trials (MDX010-020³ and CA-184-024⁴) on the assumption that GM-CSF, dacarbazine (DTIC) and gp100 (considered to be a proxy for BSC) are equally ineffective treatments in terms of OS.

For this network to yield reliable hazard ratios for comparing T-VEC and ipilimumab, it is necessary that the PH assumption is not violated within each clinical trial, nor between trials where arms from different trials are deemed to be equivalent (i.e. assumed to have a hazard ratio of 1.0). Finally, the hazard patterns of the distant comparison treatments (in this case T-VEC and ipilimumab) should also show no evidence of non-PH.

The OPTiM trial⁹ OS data for T-VEC and GM-CSF treated patients conform to the PH assumption (Figure 2). However, this is not the case when the survival profile of GM-CSF treated patients in the OPTiM trial⁹ is compared to either gp100-treated patients in MDX010-020³ (Figure 3), or to DTIC-treated patients in CA-184-024⁴ (Figure 4).

Similarly, cross-study OS comparisons of T-VEC treated patients in the OPTiM trial⁹ with ipilimumab-treated patients in MDX010-020³ (Figure 5) and with ipilimumab+DTIC treated patients in CA-184-024⁴ (Figure 6) indicate clear violations of the PH assumption.

The ERG therefore concludes that the use of the company's proposed ITC as the basis for obtaining estimated hazard ratios to calibrate a synthetic ipilimumab comparator for T-VEC cannot be considered reliable.

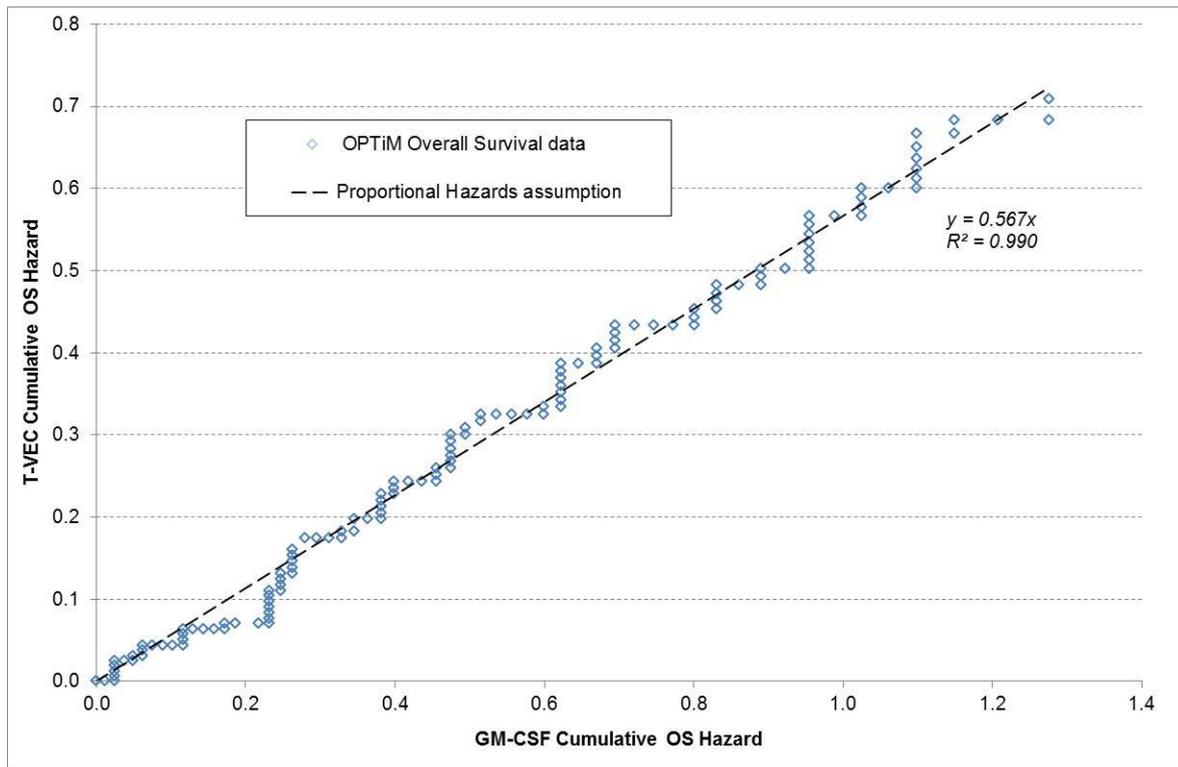


Figure 2 Proportional hazards assumption test between OS cumulative hazards in the OPTiM clinical trial (Trial observations should lie close to the PH line if OS events follow similar temporal trends in both trial arms)

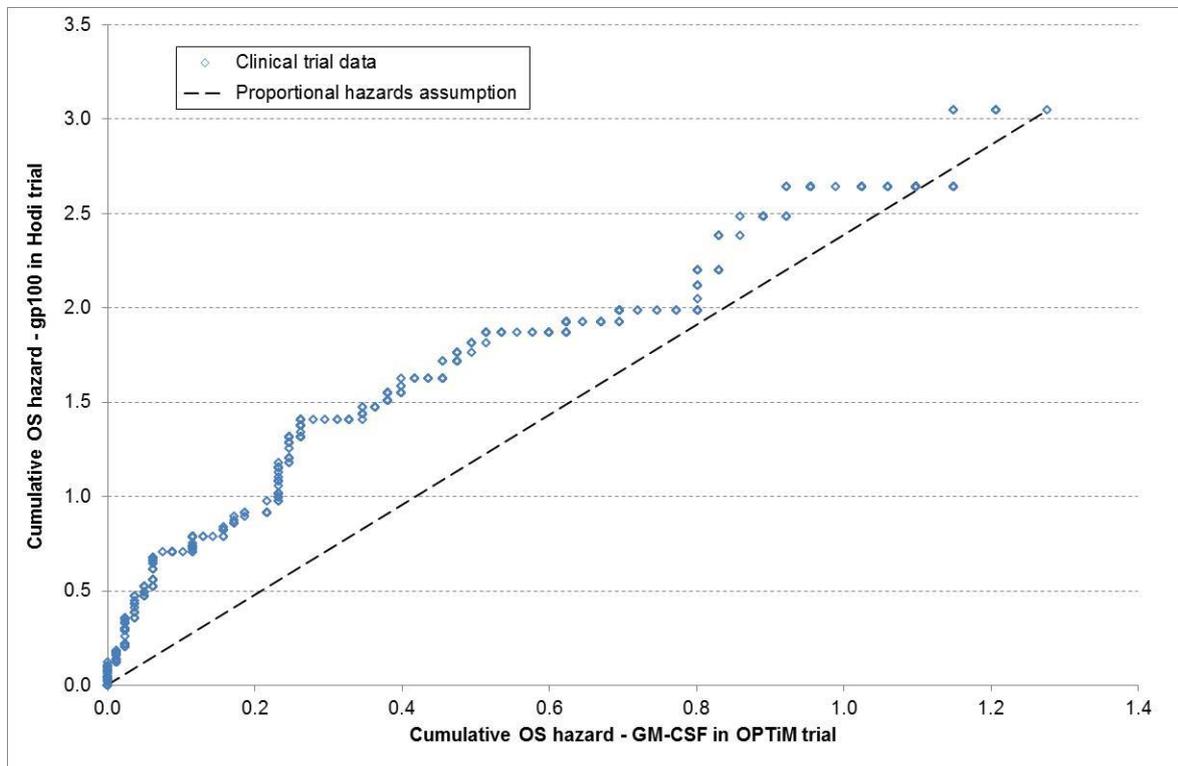


Figure 3 Proportional hazards assumption test between OS cumulative hazards in the GM-CSF arm of the OPTiM clinical trial and the gp100 arm of MDX010-020 (Trial observations should lie close to the PH line if OS events follow similar temporal trends in both trial arms)

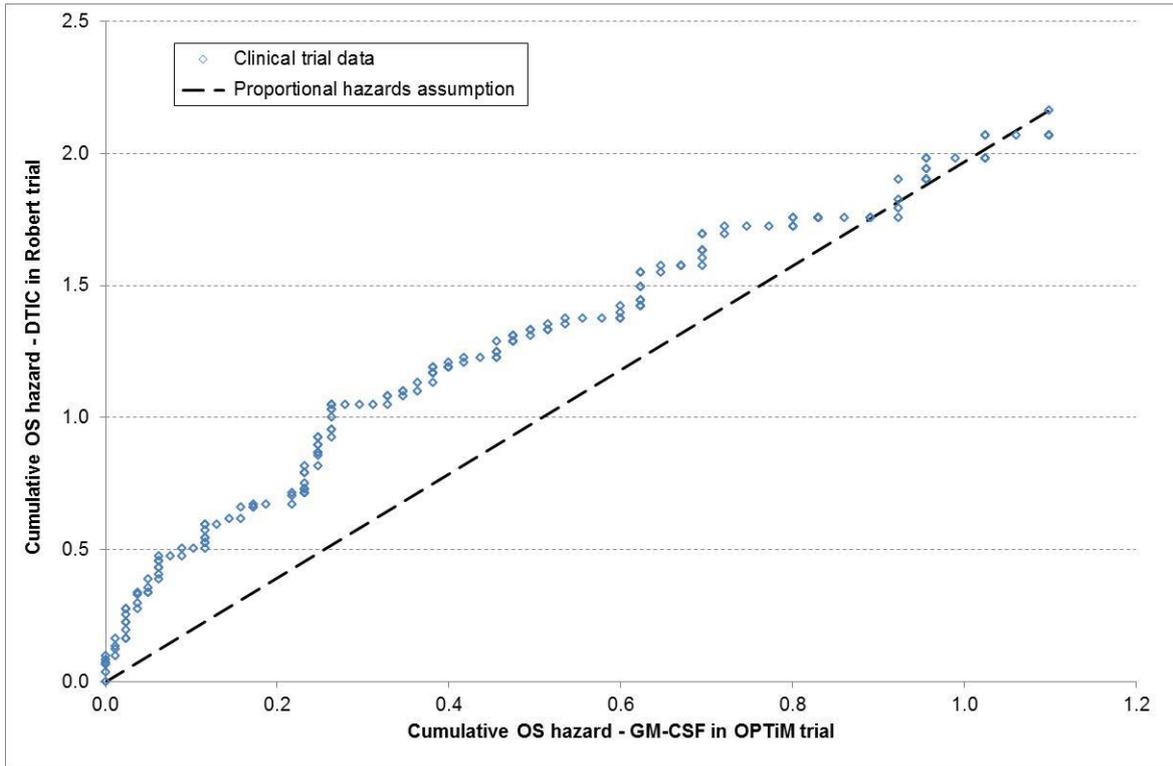


Figure 4 Proportional hazards assumption test between OS cumulative hazards in the GM-CSF arm of the OPTiM clinical trial and the DTIC arm of CA-184-024 (Trial observations should lie close to the PH line if OS events follow similar temporal trends in both trial arms)

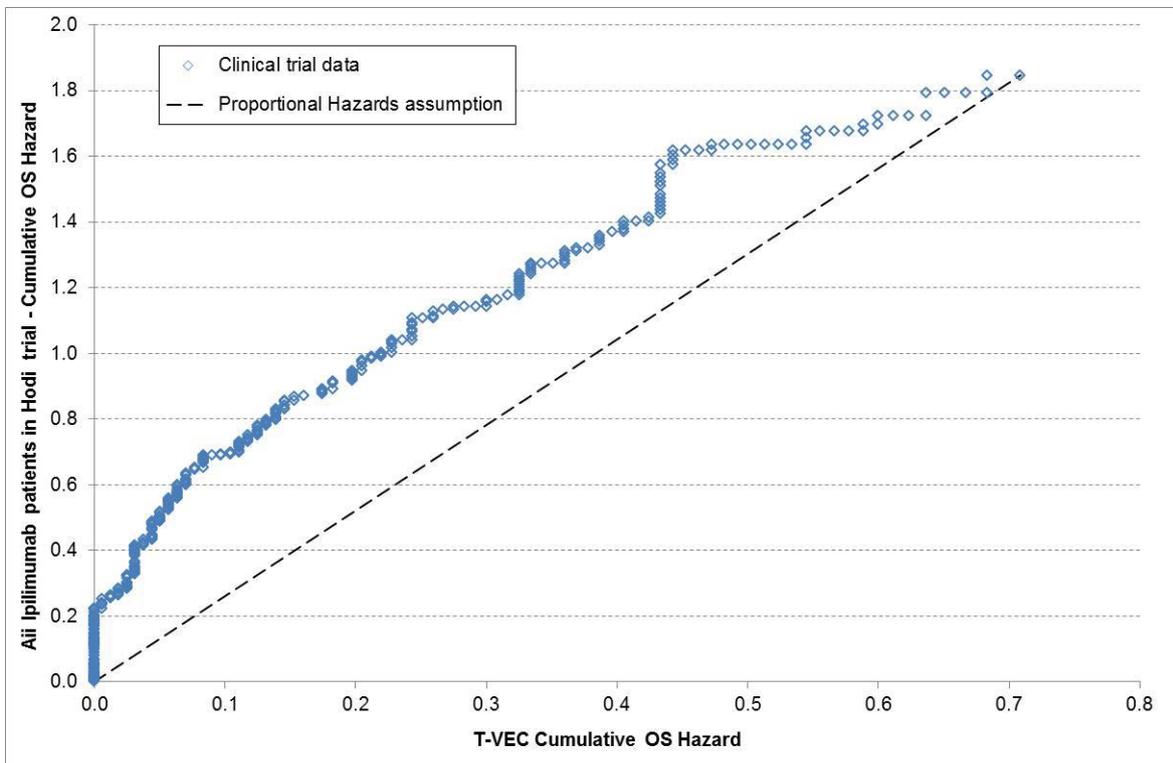


Figure 5 Proportional hazards assumption test between OS cumulative hazards in the T-VEC arm of the OPTiM clinical trial and the combined ipilimumab arms of MDX010-020 (Trial observations should lie close to the PH line if OS events follow similar temporal trends in both trial arms)

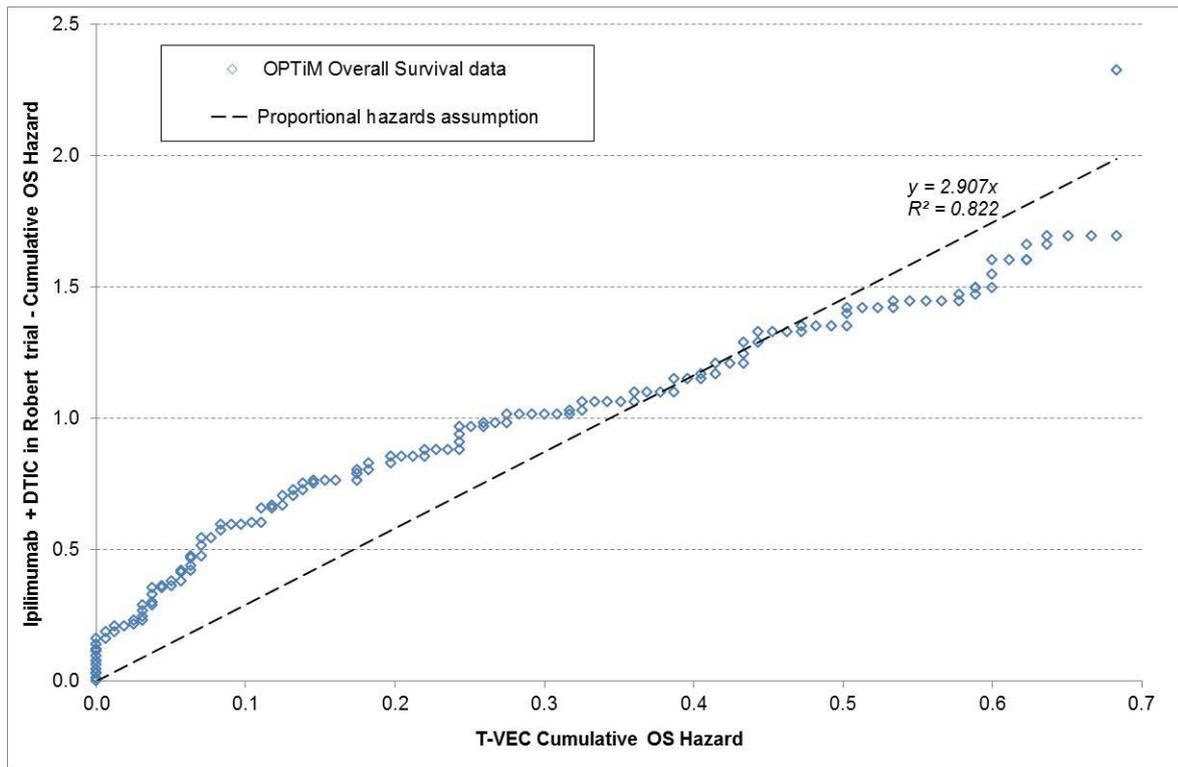


Figure 6 Proportional hazards assumption test between OS cumulative hazards in the GM-CSF arm of the OPTiM clinical trial and the ipilimumab+DTIC arm of CA-184-024 (Trial observations should lie close to the PH line if OS events follow similar temporal trends in both trial arms)

3 SURVIVAL EXTRAPOLATION

In Section 4 of the company's response to the ACD, three specific criticisms are made of the ERG's alternative method of extrapolating the survival data available from the OPTiM trial:⁹

- a. the ERG method of survival extrapolation lacks clinical validity and does not represent the OS trajectory of melanoma patients
- b. representing Kaplan-Meier (K-M) data only until the last recorded death is not appropriate and the entire K-M OS curve should be considered
- c. application of the ERG method to only T-VEC leaving the OS for ipilimumab unchanged from the company method is inappropriate.

The first challenge (a) questions the appropriateness of applying a simple exponential projective model to extend the OPTiM trial⁹ survival results for 30 years (as required by the model horizon). The company prefers to apply a trend derived from an AJCC staging database to extend survival to 10 years, then apply life table mortality estimates for a further 20 years. The AJCC data relate to a total of 38,918 patients followed-up for a maximum of 10 years from diagnosis (18,370 stage I, 9269 stage II, 3307 stage III and 7972 stage IV).

In order to consider a longer duration of follow-up in melanoma patients, the ERG has carried out analyses of the SEER database¹³ looking at OS monthly from the time of initial diagnosis for more than 16 years. Figure 7 shows the OS trajectory for all melanoma patients irrespective of initial disease stage (242,311 patients), and for those diagnosed with regional spread of disease or metastatic disease (32,978 patients), followed up for 200 months (16.7 years). In both cases the first 5 to 6 years exhibit a relatively steep loss of survival, followed by a steadier long-term trend. This appears more clearly in Figure 7 where the initial high mortality rate is superseded after 6 to 8 years by an apparently stable linear cumulative hazard trend, equivalent to a constant long-term hazard i.e. an exponential survival trend.

A straightforward parametric function has been calibrated for each of these patient populations to represent a short-term high but diminishing mortality risk superimposed on a long-term stable constant hazard, which appears to match the real-world data very closely (Figure 7 and Figure 8). It should be noted that this is not an isolated 'accidental' finding exclusive to melanoma. A similar phenomenon has been validated across a wide range of different common cancers from the SEER database¹³ including breast cancer, lung cancer, colorectal cancer, brain cancer and leukaemia.

It is not possible to give a simple explanation for this general pattern without more detailed investigations, but it seems likely that it represents an interaction between competing risk trends over an extended period including:

- initial risk heterogeneity so that those patients with a poor initial cancer prognosis and/or existing serious co-morbidities die early, leading to a progressively lower mortality rate among long-term survivors following the initial post-diagnosis period
- gradually increasing trends in unrelated mortality similar to those experienced in the general population as people age.

This has been partially confirmed in more detailed analyses of patients with breast cancer which showed that when a substantial proportion of patients reach the age of about 85 years, the linear hazard trend gradually gives way to an increasing trend similar to that in the general aged population.

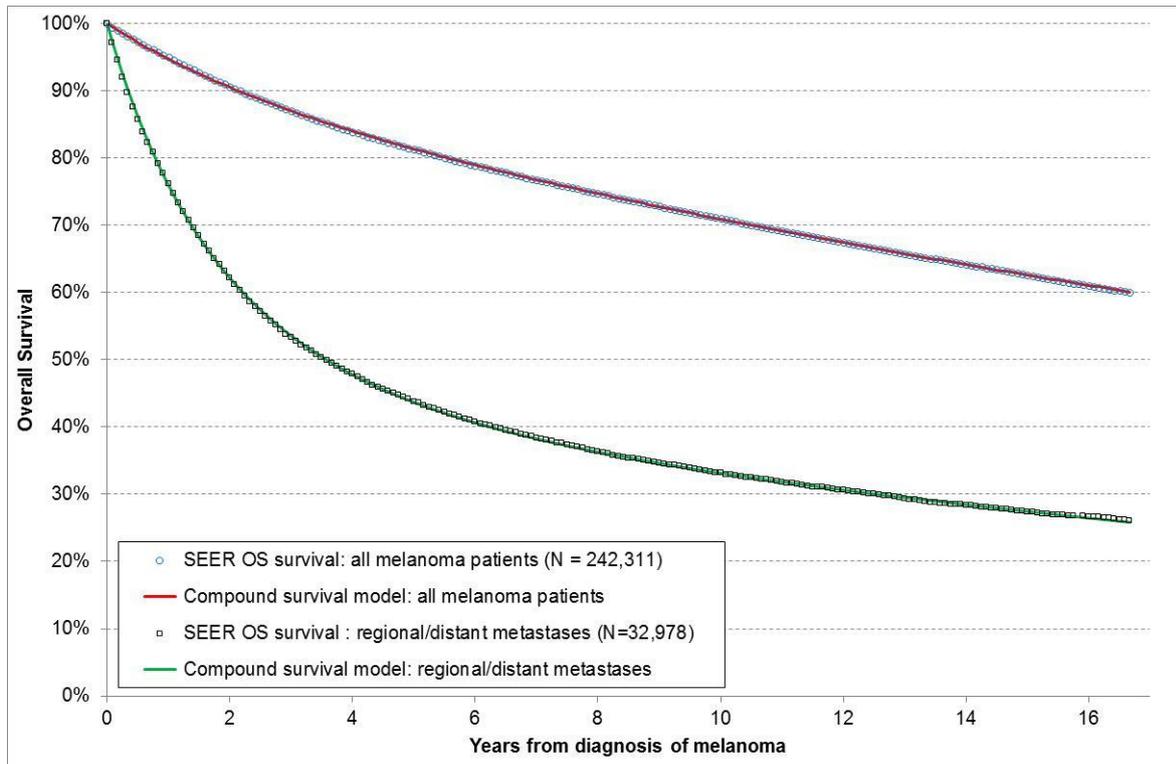


Figure 7 Overall survival of two groups of melanoma patients, with maximum follow-up greater than 16 years

A compound parametric function combining short-term high risk and a long-term stable hazard (exponential trend) is fitted accurately to each patient population.

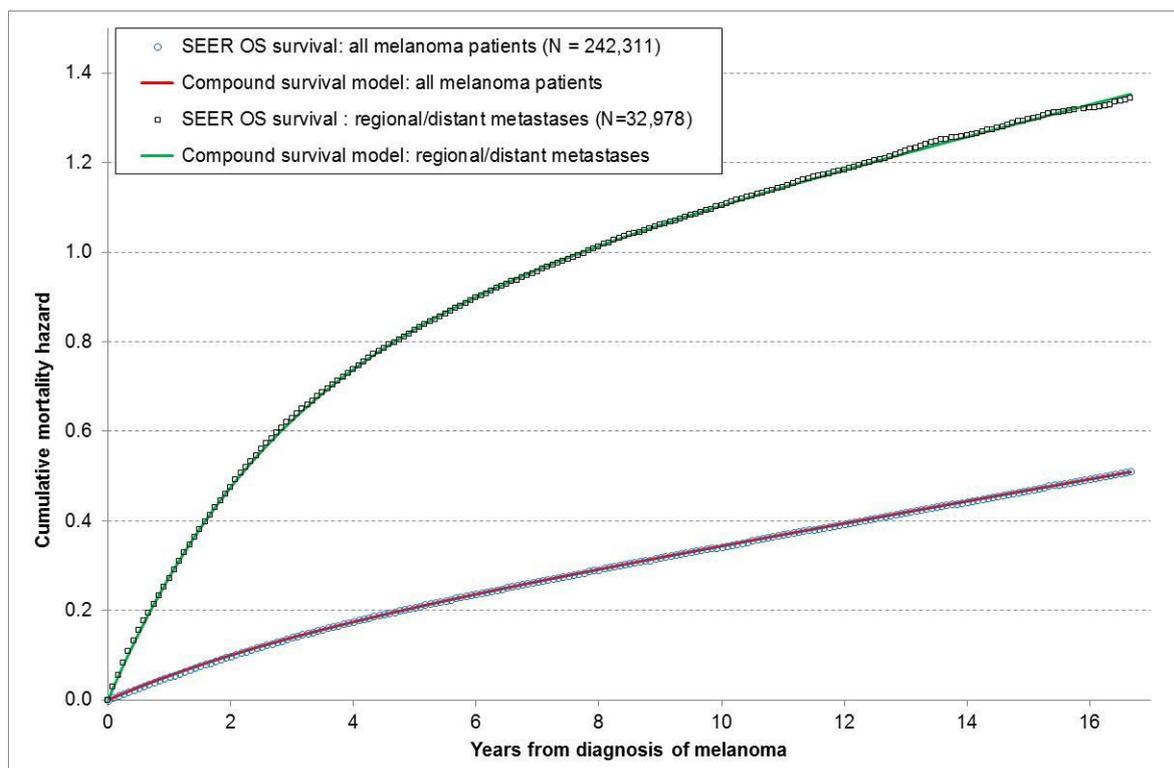


Figure 7 Cumulative mortality hazard of two groups of melanoma patients, with maximum follow-up greater than 16 years

After about 6 years, a long-term constant hazard becomes dominant over short-term high mortality risks.

The ERG therefore concludes that there is a substantial body of evidence from the SEER database¹³ that long-term exponential extrapolation of clinical trial data is appropriate in many types of cancer at least for the initial period of 16 years from initial diagnosis, thus supporting the ERG exponential projection well into the final (phase 3) period of the company's extrapolation method. Moreover, it provides a more parsimonious analytical approach than attempting to conjoin limited data from multiple contrasting sources.

The second challenge (b) concerns the OPTiM trial⁹ K-M survival data used by the ERG in fitting a 2-phase exponential function to extrapolate survival of T-VEC treated patients. The company considers that the time after the last recorded death, during which 24% of T-VEC patients continued to be followed up before being censored, should have been taken into account by the ERG, leading to a fitted model similar to that used by the company.

K-M survival estimates can only be estimated for periods in which at least one event (i.e. death) is recorded. Standard STATA, SPSS, etc. software normally generates K-M estimates at every time point (days from randomisation) for which one or more patients died. At any time after the last recorded death a meaningful K-M estimate cannot be calculated, since the interval death rate will certainly be zero, whereas we know that all of the surviving

patients are still subject to normal mortality risks – the absence of any death events in that period is merely due to chance.

The ERG has used all of the available K-M calculated survival estimates for the T-VEC trial arm on the basis that K-M is an unbiased analytic method. 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). Sadly, the ‘absence of evidence (of deaths)’ does not constitute ‘evidence of the absence of (the risk of) death’.

It is worth considering whether the ERG approach to curve fitting, based on the K-M calculated data only, is likely to be biased towards either under- or over-estimation of OS. There are very similar proportions of patients in the T-VEC trial arm who were censored prior to the time of last recorded death (26%) or later than the time of the last recorded death (24%). The average times between censoring and the last recorded death were also similar (5.5 months after the last death versus 5.2 months before the last death). This suggests that if further follow-up data become available, this is unlikely to result in additional K-M data points (i.e. deaths) which are markedly out of line with the trend used by the ERG in calibrating their exponential projection.

However, it should be borne in mind that any extra deaths that may occur in the period ***** the last recorded death among the currently censored patients will contribute to *all* subsequent K-M estimates, and are most likely to have the effect of reducing the OS estimates for the *whole* of the subsequent analysis (including the last death event in the current data cut). Thus, there is a significant chance that the OS estimates for T-VEC from the latest data cut (8 August 2014) may in fact prove to be over-optimistic when additional follow-up data are available.

In summary, the ERG is confident that confining attention to the K-M analysis results for trial deaths is the correct method to adopt, and that any attempt to anticipate later trends from limited censored data risks seriously over-estimating long-term survival.

The third challenge (c) is that the ERG has only applied their projection method to treatment with T-VEC, and not to the synthetic ipilimumab comparator.

The ERG made very clear in their report¹⁴ that they did not believe that the company's method of generating a synthetic ipilimumab comparator was reliable. The company's method involves pooling trial data from trials in different populations, and then applying questionable case-mix adjustment hazard ratios, followed by registry trends, and life table

mortality rates in an arbitrary fashion. There was nothing to be gained from manipulating the individual components of this unrealistic construct, as it serves only to accord it apparent credibility that it does not warrant.

The modelling of the T-VEC trial data should be considered only as a sensitivity analysis to demonstrate that using different assumptions and analytic methods for the long-term outcome prospects in at least one part of the company's decision model could lead to very different cost effectiveness results.

4 COST EFFECTIVENESS OF T-VEC VERSUS RECOGNISED TREATMENTS AND BSC

The company has presented results of an additional cost effectiveness analysis comparing T-VEC with DTIC and BSC in its response to the ACD.

In this section the ERG presents the results of a re-analysis of the company's additional cost effectiveness analysis. The ERG has applied model modifications that were previously described in the ERG report¹⁴ together with the effectiveness assumptions (that GM-CSF is at least as effective as DTIC and gp100/BSC) for the two additional comparators, and using the latest version of the company decision analysis model.

4.1 *Assumptions for additional comparators: effectiveness and treatment costs*

4.1.1 Effectiveness and safety outcomes

It is assumed that all effectiveness and safety data derived from the comparator arm (GM-CSF) of the OPTiM trial⁹ and used to populate the company model are also applicable to the two alternative comparators (DTIC and BSC).

4.1.2 Treatment costs

The drug acquisition cost and administration cost of treatment with DTIC should be estimated for an equivalent UK population, and no treatment costs should be included for the BSC comparator.

An exploratory review of publicly available treatment guidelines from English health commissioning groups indicates that the most commonly used DTIC regimen is 850mg per m² of body surface area (BSA) administered every 3 weeks for up to a maximum of six cycles. The ERG has estimated the mean acquisition cost per dose of DTIC based on a typical distribution of BSA in English cancer patients,¹⁵ stratified by gender but assuming the same gender balance (males:females) as in the OPTiM trial.⁹ Since DTIC is available as a generic product to NHS providers, the current average price paid in the NHS has been used (rather than the list price).¹⁶ This results in an overall weighted average cost per dose of DTIC of £52.49. For a course of six cycles of DTIC the ERG estimated drug acquisition cost is £241.41 per patient and the administration cost is £1,457.59 per patient, giving a total cost of £1,699 per patient.

4.2 ERG model amendments previously identified

4.2.1 Lifetime overall survival and progression-free survival

The company model is based on a complex concatenation of four time phases each calibrated from different sources to estimate survival profiles for up to 30 years. Instead, the ERG proposes the direct use of trial-based OS and PFS K-M analysis data followed by long-term exponential (constant risk) extrapolation modelling. The wide divergence between the estimates generated by these two approaches is apparent from Figure 8 (Figure 8 in the original ERG report¹⁴). A full critique of the company's approach is presented in the original ERG report,¹⁴ concluding that the company model may overestimate the mean OS for patients receiving T-VEC by 49% to 59%. The ERG's preferred estimation method for estimating long-term mean OS and PFS per patient has been applied as an option in the latest version of the company model to allow a sensitivity analysis to be performed.

4.2.2 Discounting

The company model applies discounting to costs and outcomes on a continuous (weekly) basis, rather than annually in line with NHS budgeting and accounting years. This has the effect of reducing treatment acquisition and administration costs during the first year for both intervention and comparator, as well as reducing the QALYs associated with both treatments. The ERG applied annual discounting as an option in the latest version of the company model to allow a sensitivity analysis to be performed.

4.2.3 Health state utility values

In the company's base case analysis, health state utility values are taken from the NICE appraisal of dabrafenib (TA321)⁶ in preference to the values obtained by the company from a commissioned study¹⁷ (CS, Appendix 1.7). It is the ERG's considered opinion that the values obtained from the commissioned study¹⁷ have greater face validity than those used in the base case analysis. In particular, the TA321⁶ values poorly differentiate between distinct health states: there is no difference between values assigned to complete response, partial response and stable disease. The ERG has applied these values as an option in the latest version of the company model to allow a sensitivity analysis to be performed.

4.2.4 Continuity correction

The company employs a half-cycle correction in their decision model for the estimation of outcomes and some costs. This method is recognised to be inaccurate except in particular circumstances. The ERG has applied the more generally applicable mid-cycle correction to the affected model outcomes as an option in the latest version of the company model to allow a sensitivity analysis to be performed.

4.2.5 Terminal disutility

The company model does not differentiate the estimated health related quality of life (HRQoL) applicable to patients in the progressed disease (PD) state (which can last for an extended period) from the condition of patients in terminal care (usually considered as the last 2 weeks of life). The utility value estimated in the commissioned utility study¹⁷ (CS, Appendix 1.7) for the BSC state to the last 2 weeks of life has been applied as an option in the latest version of the company model to allow a sensitivity analysis to be performed.

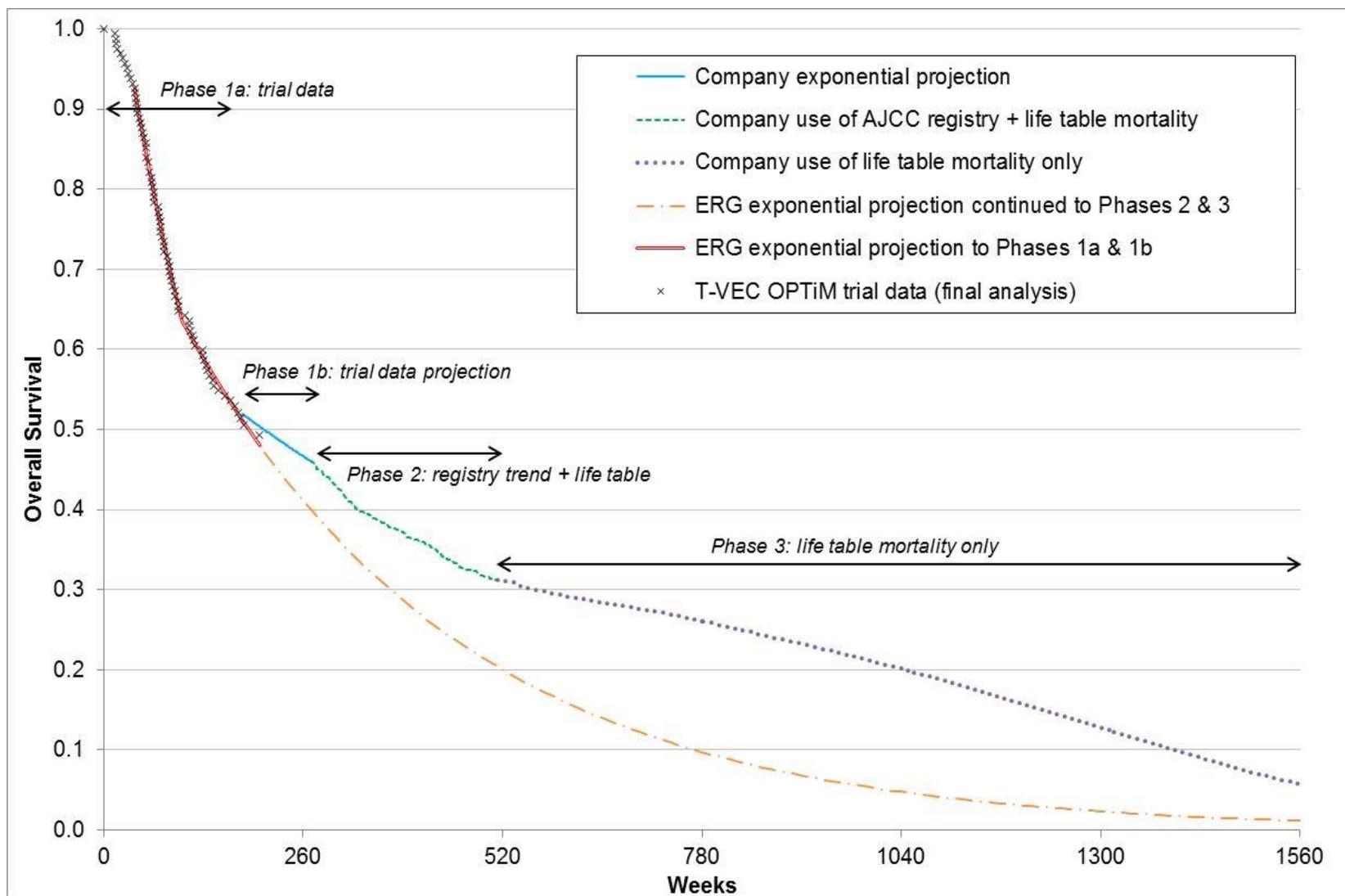


Figure 8 Company long-term T-VEC OS projection compared to ERG simple exponential alternative projection

4.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Tables 1 to 4 summarise the effect on the cost effectiveness of T-VEC compared to DTIC and BSC on the assumption that DTIC and BSC are equivalent to GM-CSF in terms of survival, response to treatment and adverse events. The effects of seven model amendments proposed by the ERG are exemplified individually and in combination. In each table the net effect of applying all of the model amendments is to produce a modest increase in the size of the estimated ICER per QALY gained.

Table 1 Cost effectiveness (T-VEC vs DTIC): ERG revisions to company base case (T-VEC list price, DTIC generic NHS price)

Model scenario / ERG revision	T-VEC			DTIC			Incremental			ICER £/QALY	ICER Change
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years		
A. Company base case	████	4.762	9.039	████	2.785	5.200	████	+1.978	+3.838	████	█
R1) ERG OS extrapolation	████	3.613	6.063	████	2.113	3.450	████	+1.500	+2.614	████	████
R2) ERG PFS extrapolation	████	4.813	9.039	████	2.831	5.200	████	+1.982	+3.839	████	█
R3) Annual discounting	████	4.843	9.039	████	2.831	5.200	████	+2.012	+3.838	████	█
R4) Commissioned health state utility values	████	3.731	9.039	████	1.942	5.200	████	+1.788	+3.838	████	████
R5) ERG continuity correction	████	4.748	9.009	████	2.776	5.183	████	+1.972	+3.826	████	█
R6) Include terminal disutility	████	4.757	9.039	████	2.778	5.200	████	+1.979	+3.838	████	█
R7) UK BSA values	████	4.762	9.039	████	2.785	5.200	████	+1.978	+3.838	████	█
B. ERG revised base case A+R1-R7	████	3.164	6.043	████	1.635	3.438	████	+1.528	+2.605	████	████

Costs and QALYs discounted; life years undiscounted

ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; BSA=body surface area

Table 2 Cost effectiveness (T-VEC vs BSC): ERG revisions to company base case (T-VEC list price)

Model scenario / ERG revision	T-VEC			BSC			Incremental			ICER £/QALY	ICER Change
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years		
A. Company base case	████	4.762	9.039	████	2.785	5.200	████	+1.978	+3.838	████	█
R1) ERG OS extrapolation	████	3.613	6.063	████	2.113	3.450	████	+1.500	+2.614	████	████
R2) ERG PFS extrapolation	████	4.813	9.039	████	2.831	5.200	████	+1.982	+3.839	████	█
R3) Annual discounting	████	4.843	9.039	████	2.831	5.200	████	+2.012	+3.838	████	█
R4) Commissioned health state utility values	████	3.731	9.039	████	1.942	5.200	████	+1.788	+3.838	████	████
R5) ERG continuity correction	████	4.748	9.009	████	2.776	5.183	████	+1.972	+3.826	████	█
R6) Include terminal disutility	████	4.757	9.039	████	2.778	5.200	████	+1.979	+3.838	████	█
R7) UK BSA values	████	4.762	9.039	████	2.785	5.200	████	+1.978	+3.838	████	█
B. ERG revised base case A+R1-R7	████	3.164	6.043	████	1.635	3.438	████	+1.528	+2.605	████	████

Costs and QALYs discounted; life years undiscounted

ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; BSA=body surface area; BSC=best supportive care

Table 3 Cost effectiveness (T-VEC vs DTIC): ERG revisions to company base case (T-VEC PAS price, DTIC generic NHS price)

Model scenario / ERG revision	T-VEC			DTIC			Incremental			ICER £/QALY	ICER Change
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years		
A. Company base case	■	4.762	9.039	■	2.785	5.200	■	+1.978	+3.838	23,919	-
R1) ERG OS extrapolation	■	3.613	6.063	■	2.113	3.450	■	+1.500	+2.614	29,442	+5,523
R2) ERG PFS extrapolation	■	4.813	9.039	■	2.831	5.200	■	+1.982	+3.839	24,110	+191
R3) Annual discounting	■	4.843	9.039	■	2.831	5.200	■	+2.012	+3.838	23,580	-339
R4) Commissioned health state utility values	■	3.731	9.039	■	1.942	5.200	■	+1.788	+3.838	26,542	+2,533
R5) ERG continuity correction	■	4.748	9.009	■	2.776	5.183	■	+1.972	+3.826	23,993	+74
R6) Include terminal disutility	■	4.757	9.039	■	2.778	5.200	■	+1.979	+3.838	23,904	-15
R7) UK BSA values	■	4.762	9.039	■	2.785	5.200	■	+1.978	+3.838	23,936	+17
B. ERG revised base case A+R1-R7	■	3.164	6.043	■	1.635	3.438	■	+1.528	+2.605	29,303	+5,384

Costs and QALYs discounted; life years undiscounted

ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; BSA=body surface area

Table 4 Cost effectiveness (T-VEC vs BSC): ERG revisions to company base case (T-VEC PAS price)

Model scenario / ERG revision	T-VEC			BSC			Incremental			ICER £/QALY	ICER Change
	Cost £	QALYs	Life years	Cost £	QALYs	Life years	Cost £	QALYs	Life years		
A. Company base case	■	4.762	9.039	■	2.785	5.200	■	+1.978	+3.838	24,805	-
R1) ERG OS extrapolation	■	3.613	6.063	■	2.113	3.450	■	+1.500	+2.614	30,610	+5,805
R2) ERG PFS extrapolation	■	4.813	9.039	■	2.831	5.200	■	+1.982	+3.839	24,994	+189
R3) Annual discounting	■	4.843	9.039	■	2.831	5.200	■	+2.012	+3.838	24,451	-354
R4) Commissioned health state utility values	■	3.731	9.039	■	1.942	5.200	■	+1.788	+3.838	27,431	+2,627
R5) ERG continuity correction	■	4.748	9.009	■	2.776	5.183	■	+1.972	+3.826	24,881	+76
R6) Include terminal disutility	■	4.757	9.039	■	2.778	5.200	■	+1.979	+3.838	24,789	-15
R7) UK BSA values	■	4.762	9.039	■	2.785	5.200	■	+1.978	+3.838	24,805	0
B. ERG revised base case A+R1-R7	■	3.164	6.043	■	1.635	3.438	■	+1.528	+2.605	30,427	+5,622

Costs and QALYs discounted; life years undiscounted

ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; BSA=body surface area; BSC=best supportive care

5 POST-HOC SUBGROUPS

In its original report,¹⁴ the ERG noted that: “although subgroup analyses by different stages of disease (stage IIIB to IIIC, stage IV M1a, stage IV M1b and stage IV M1c) were all pre-specified [in the OPTiM trial⁹], stage IIIB to stage IV M1a disease was not a pre-specified subgroup but rather defined post-hoc.” Concerns with post-hoc analyses are usually related to issues with ‘data fishing’ in which results can be presented as being statistically significant when they may have only occurred by chance. In this instance, the ERG was less concerned by issues of ‘data fishing’ since the results for the primary endpoint (durable response rate) for the OPTiM trial⁹ showed statistically significant improvements for patients treated with T-VEC compared with GM-CSF in both the subgroup of patients with stage IIIB to IIIC and the subgroup of patients with stage IV M1a disease. Indeed the ERG recognises that the credibility of the subgroup was discussed with the European Medicines Agency (EMA) and that the EMA were satisfied with the subgroup, hence the granting of a marketing authorisation for this group of patients.

Of greater concern to the ERG, particularly in relation to extrapolating survival data over time, was that the disease survival trajectory of patients with stage IIIB to IIIC disease was considered likely to differ to that of patients with stage IV M1a disease; indeed, the difference in OS between trial arms was statistically significantly in favour of T-VEC compared with GM-CSF for patients with stage IIIB to IIIC disease but not stage IV M1a disease. However, the company has argued that SEER data “show that the disease trajectory is similar in those with stage IIIB/C and IVM1a disease (Song et al, 2015.^[18])” The ERG’s analysis of digitized data displayed in the Song et al 2015 paper¹⁸ indicates that there is no discernible difference in survival patterns between patients with stage IIIB to IIIC disease and patients with stage IV M1a disease.

6 SUMMARY

A summary of the company's arguments and ERG review of the arguments is presented below.

1. The Korn methods, used to evaluate comparative effectiveness in earlier stage disease, are suitable to adjust ipilimumab survival data to the earlier stage population. They are sufficiently robust and consistently conservative in favour of ipilimumab; presenting a range of estimates that show T-VEC is at least as effective as ipilimumab in the worst-case scenario.

For the 'modified Korn model' to be valid for adjusting patient outcomes for ipilimumab as an active comparator, the model would need to be calibrated against patient-level data from trials of ipilimumab in similar patient populations, but there is no indication in the company submission (CS) that this is the case. Furthermore, if it is assumed that the model is valid, it is unclear if the calculation of hazard ratios and adjustment factors have been correctly applied. Certainly the model used for PFS is questionable as the company has used a model for OS to model PFS but the ERG have shown that OS and PFS hazards occur at very different times.

2. Analyses using Korn methods to evaluate comparative efficacy in the broader population of patients including later stage disease, support the case that T-VEC is at least as effective as ipilimumab.

The ERG has not explored this issue since as highlighted above, even if the modified Korn model could be assumed to be valid, it is unclear if the calculation of hazard ratios and adjustment factors have been correctly applied.

3. Analysis using conventional indirect treatment comparison (ITC) methods to compare T-VEC with ipilimumab in earlier stage disease also shows that T-VEC is at least as effective as ipilimumab; supporting the findings using Korn methods, and providing external validity.

To yield reliable hazard ratios for comparing T-VEC and ipilimumab, it is necessary that the PH assumption is not violated within each clinical trial, nor between trials where arms from different trials are deemed to be equivalent (i.e. assumed to have a hazard ratio of 1.0). The hazard patterns of the distant comparison treatments (in this case T-VEC and ipilimumab)

should also show no evidence of non-PH. However, the ERG found the PH assumption is violated. **The ERG therefore concludes that the use of the company's proposed ITC as the basis for obtaining estimated hazard ratios to calibrate a synthetic ipilimumab comparator for T-VEC cannot be considered reliable.**

4. Cost effectiveness analysis show that T-VEC is cost effective versus ipilimumab even when using the ERG method for OS extrapolation; provided that it is consistently applied to both treatments.

The ERG did not believe that the company's method of generating a synthetic ipilimumab comparator was reliable. Hence the ERG only modelled T-VEC trial data as a sensitivity analysis to demonstrate that using different assumptions and analytic methods for the long-term outcome prospects in at least one part of the company's decision model could lead to very different cost effectiveness results.

5. There is robust evidence of clinical and cost effectiveness of T-VEC versus recognised treatments (dacarbazine [DTIC]) and best supportive care (BSC) but with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that T-VEC is cost effective versus ipilimumab.

The company assumes that DTIC and BSC are of equal efficacy to GM-CSF and reported ICERs of £23,919 and £24,094 per QALY gained versus DTIC and BSC respectively. The ERG made seven amendments to the company's model: (1) applying an alternative method for extrapolating OS based on the SEER database¹³ (2) applying an alternative method for extrapolating PFS (3) applying annual as opposed to weekly discounting (4) applying alternative utility values from a study commissioned by the company¹⁷ as opposed to those derived from the NICE appraisal of dabrafenib (TA321)⁶ (5) applying a mid-cycle correction as opposed to a half-cycle correction (6) including terminal disutility from the aforementioned study commissioned by the company¹⁷ (7) applying treatment costs based on BSA values. The net effect of applying all of the model amendments is to produce a modest increase in the size of the estimated ICER per QALY gained (or around █████ per QALY gained using the list price for T-VEC vs each comparator or around £5,000 per QALY gained using the PAS price for T-VEC vs each comparator).

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