

**5.11 Talimogene laherparepvec  
Intra-lesional injection, 1 million and 100 million PFU/mL  
Imlygic™  
Amgen Australia Pty Ltd**

**1 Purpose of Application**

1.1 Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (Streamlined) listing for the treatment of unresectable stage III or stage IV malignant melanoma without visceral metastases.

**2 Requested listing**

2.1 The requested restriction is provided below, including initial and continuing treatment criteria. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

**Talimogene laherparepvec injection 1 million PFU/mL: initial treatment (*BRAF* positive)**

Name, Restriction, Manner of administration and form	Max Amnt	No.of Rpts	DPMA	Brand name and manufacturer
Talimogene laherparepvec Injection 1 million PFU/mL, 1 mL vial	4 million PFU	0	\$13,000.95 Public \$13,214.33 Private	Imlygic™ AN

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Unresectable Stage III or IVM1a</i>
Condition:	malignant melanoma
PBS Indication:	<del>Injectable</del> , <i>Unresectable Stage III or Stage IVM1a malignant melanoma without visceral metastases</i>
Treatment phase:	Initial treatment <i>1</i>
Restriction Level/Method	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority required – In writing <input type="checkbox"/> Authority required – Telephone <input type="checkbox"/> Authority required – Emergency <input type="checkbox"/> Authority required – Electronic <input checked="" type="checkbox"/> Streamlined

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<p>Clinical criteria:</p>	<p><i>Patient must have undergone surgery,</i></p> <p><i>AND</i></p> <p><i>The condition must be positive for a BRAF V600 mutation,</i></p> <p><i>AND</i></p> <p><i>The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information,</i></p> <p><i>AND</i></p> <p><i>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition,</i></p> <p><i>AND</i></p> <p><i>The treatment must be the sole PBS-subsidised therapy for this condition.</i></p>
<p><i>Prescriber Instruction</i></p>	<p><i>A maximum of 4 mL to be injected (4 x 1 mL)</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p>
<p><i>Administrative advice</i></p>	<p><i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i></p>

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**Talimogene laherparepvec injection 1 million PFU/mL: initial treatment (BRAF negative)**

Name, Restriction, Manner of administration and form	Max Amnt	No. of Rpts	DPMA	Brand name and manufacturer
Talimogene laherparepvec Injection 1 million PFU/mL, 1 mL vial	4 million PFU	0	\$13,000.95 Public \$13,214.33 Private	Imlygic™ AN

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Unresectable Stage III or IVM1a</i>
Condition:	malignant melanoma
PBS Indication:	<del>Injectable</del> , Unresectable Stage III or Stage IVM1a malignant melanoma <del>without visceral metastases</del>
Treatment phase:	Initial treatment 2
Restriction Level/Method	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority required – In writing <input type="checkbox"/> Authority required – Telephone <input type="checkbox"/> Authority required – Emergency <input type="checkbox"/> Authority required – Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<i>Patient must have undergone surgery,</i>  <i>AND</i>  <i>The condition must be negative for a BRAF V600 mutation,</i>  <i>AND</i>  <i>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition,</i>  <i>AND</i>  <i>The treatment must be the sole PBS-subsidised therapy for this condition.</i>
Prescriber Instruction	<i>A maximum of 4 mL to be injected (4 x 1 mL)</i> <i>No increase in the maximum number of repeats may be authorised.</i> <i>No increase in the maximum quantity or number of units may be authorised.</i>
Administrative Advice	<i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i>

**Talimogene laherparepvec injection 100 million PFU/mL: continuing treatment**

Name, Restriction, Manner of administration and form	Max Amnt	No. of Rpts	DPMA	Brand name and manufacturer
Talimogene laherparepvec Injection 100 million PFU/mL, 1 mL vial	400 million PFU	4412	\$13,000.95 Public \$13,214.33 Private	Imlygic™ AN

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Unresectable Stage III or Stage IVM1a</i>
Condition:	Malignant melanoma
PBS Indication:	<del>Injectable</del> , Unresectable Stage III or Stage IVM1a malignant melanoma <del>without visceral metastases</del>
Treatment phase:	Continuing treatment
Restriction Level/Method	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority required – In writing <input type="checkbox"/> Authority required – Telephone <input type="checkbox"/> Authority required – Emergency <input type="checkbox"/> Authority required – Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria	Patient must have previously been issued with an authority prescription for <i>this drug for this condition</i> , <del>talimogene laherparepvec 10<sup>6</sup> PFU/mL</del>  AND  The treatment must be the sole PBS-subsidised therapy for this condition,  AND  <i>Patient must have stable or responding disease.</i>
Prescriber Instruction	A maximum of 4 mL to be injected at each visit No increase in the maximum number of repeats <del>will</del> be authorised. <i>No increase in the maximum quantity or number of units may be authorised.</i>
Administrative advice	<i>In the first few months after start of immunotherapy some patients can have a transient tumour flare with subsequent disease response. When progression is suspected this should be confirmed through a confirmatory scan taken at least 4 weeks later.</i>

2.2 The requested PBS listing was for patients with unresectable melanoma who do not have visceral metastases, to correspond to a subgroup analysis of participants in the key trial with stage IIIb/c and stage IVM1a melanoma. The approved TGA indication for talimogene laherparepvec (T-VEC) is for the treatment of unresectable melanoma in patients with cutaneous, subcutaneous or nodal lesions after initial surgery. The ESC considered that, by excluding stage IVM1b and IVM1c, this proposed population would be smaller than that of the nominated comparators. Given the usual rate of

progression, there would also be only a small window of time between developing unresectable melanoma and then developing visceral metastases. The ESC was concerned with the risk of not identifying subclinical visceral metastases and therefore sub-optimal outcomes from T-VEC therapy. The pre-PBAC response noted that the window of time is variable and patient specific, and that some unresectable will experience a delay to visceral metastases as a result of T-VEC treatment (17% complete responses in the proposed subgroup).

- 2.3 The requested listing did not include any requirements in relation to prior therapy. This was similar to the ipilimumab PBS restriction for induction treatment, but differed from the PBS restrictions for initial treatment with pembrolizumab and nivolumab, which require that patients with a *BRAF* V600 mutation must have progressed following prior treatment with a *BRAF* inhibitor (with or without a MEK inhibitor), and all patients must not have received prior ipilimumab or PD-1 inhibitor for melanoma. The requested listing also differed from that for pembrolizumab and the listing recommended for nivolumab in that it sought to restrict the use of T-VEC to patients without visceral metastases, effectively excluding patients with stage IVM1b and IVM1c melanoma. The Pre-Sub-Committee Response (PSCR) agreed with the Secretariat suggestion for separate initial restrictions for patients who are positive and negative for *BRAF* V600 mutation.
- 2.4 The submission sought listing on the basis of a cost-minimisation analysis of T-VEC compared to ipilimumab (as a proxy for pembrolizumab). The submission stated that since the comparators are listed on the PBS with a special pricing arrangement (SPA), it is anticipated that a confidential rebate for T-VEC will be negotiated with the Department of Health following a positive PBAC recommendation. The submission did not provide a requested effective price for T-VEC. The PBAC considered that there was insufficient basis for the cost-minimisation analysis of T-VEC compared to ipilimumab as the submission did not establish whether T-VEC was inferior or non-inferior to ipilimumab.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### **3 Background**

- 3.1 T-VEC was registered by the TGA on 21 December 2015 as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous and nodal lesions after initial surgery.
- 3.2 This was the first consideration of T-VEC by the PBAC. The PBAC has recently considered ipilimumab (November 2012), vemurafenib (March 2013), dabrafenib (July 2014), trametinib (November 2014), pembrolizumab (March 2015) and nivolumab (November 2015) for the treatment of unresectable stage III or stage IV metastatic melanoma.

### **4 Clinical place for the proposed therapy**

- 4.1 The submission reported that unresectable stage III or metastatic stage IV melanoma has a poor prognosis, with median survival of 5 to 24 months depending on the stage

of disease, with the lowest survival rate being in patients with stage IVM1c disease. Survival rates based on the American Joint Committee on Cancer (AJCC) Melanoma Staging Database range from 24% to 68% for 10-year survival for stage III and 10% to 15% for stage IV. These estimated survival rates pre-date the PBS listing of pembrolizumab, ipilimumab and dabrafenib and consequently may not reflect the prognosis with current treatment.

- 4.2 For patients who test negative for a *BRAF* V600 mutation (*BRAF* wild-type), treatment with pembrolizumab or nivolumab (PD-1 inhibitors) or ipilimumab is received as first-line therapy. For patients who test positive for a *BRAF* mutation, treatment with a *BRAF* inhibitor and MEK inhibitor is received as first-line therapy. For patients with cutaneous and/or subcutaneous lesions without visceral metastases, intra-lesional therapies such as BCG (Bacillus, Calmette and Guerin strain of mycobacterium bovis) can also be used; however these therapies are not PBS-subsidised. The submission proposed in its Section E.3 that PBS-subsidised T-VEC would mainly substitute for pembrolizumab. It is likely that T-VEC would be used as first-line therapy in patients without a *BRAF* mutation and possibly as second-line therapy in patients with a *BRAF* mutation. There would also be a potential for first-line use in patients with the *BRAF* mutation and a potential for use following pembrolizumab, nivolumab or ipilimumab.
- 4.3 The ESC considered that, in practice, T-VEC would be more complex to administer than existing therapy options, requiring specialist cancer centres, and additional time in counting, measuring and injecting each set of lesions at each therapy visit, including the use of ultrasound as necessary. The ESC also considered that, although the PSCR (p2) confirmed that the Office of Gene Technology Regulator (OGTR) had not imposed specific measures to manage any risks in the commercial supply or disposal of T-VEC, standard work health and safety procedures would be invoked by healthcare facilities. These procedures would include infection control measures to minimise the risk of herpetic spread from potential exposure to T-VEC as a consequences of viral shedding. The risk of potential exposure would apply to immunocompromised patients who would attend the treatment facility and also to healthcare workers who would handle T-VEC. Managing these issues add to the complexity of using T-VEC and hence the need for specialist centres with dedicated, trained staff and facilities for safe storage and disposal of T-VEC. The Pre-PBAC response indicated that the requirements to use T-VEC safely are consistent with standard measures of good clinical practice and universal precautions. The PBAC agreed with the ESC's views that T-VEC would be more complex to administer than existing therapy options.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **5 Comparator**

- 5.1 The submission nominated pembrolizumab, nivolumab and ipilimumab as comparators, with ipilimumab as the comparator for pricing purposes. The nominated comparators were appropriate. The ESC considered that, in practice, T-VEC would likely displace the nominated comparators, rather than replace them. The PBAC agreed with the ESC's views, and considered that BRAF/MEK inhibitors (such as dabrafenib with trametinib), and intra-lesional BCG, were also relevant comparators.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with T-VEC including the loco-regional control of melanoma, and as an extra treatment option in patient management.
- 6.3 The PBAC noted the comments received from the Australia and New Zealand Melanoma Trials Group (ANZMTG) and Melanoma Patients Australia (MPA) on the use of T-VEC in clinical practice. The PBAC particularly noted the comments that the use of T-VEC was well tolerated, and represented a new and different mode of action and treatment option. The ANZMTG stated that T-VEC had demonstrated overall survival in the proposed (early stage metastatic) PBS population. The MPA noted that, given T-VEC was a live virus, patients would need to be educated on proper handling and wound dressing. The PBAC noted that the comments received from the health professionals, ANZMTG and MPA were consistent with, and complementary to, the evidence provided in the submission.

### ***Clinical trials***

- 6.4 The submission was based on an informal comparison of one trial comparing T-VEC and GM-CSF (OPTiM), a second trial comparing nivolumab and dacarbazine (DTIC) (CA209-066), and a third trial comparing ipilimumab and gp100 (glycoprotein 100) (MDX010-20). The submission claimed that since GM-CSF, DTIC and gp100 both represent largely ineffective therapies, that these therapies represent a common reference. The PBAC agreed with the ESC that GM-CSF is ineffective. The submission also presented supporting data on T-VEC from a non-comparative trial of T-VEC (study 002/03), and from two trials of pembrolizumab; one of these comparing pembrolizumab and ipilimumab (KN-006), and the other comparing different doses of pembrolizumab (KN-001).

6.5 Details of the trials presented in the submission are provided in Table 1.

**Table 1: Trials (and associated reports) presented in the submission**

Trial	Description	Reports	Exchangeable?
Talimogene laherparepvec			
OPTiM (Study 005/05 and 005/05-E)	R, OL, MC	A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX <sup>GM-CSF</sup> Compared to Subsequently Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIB, IIIC and IV Disease.  An Extension Protocol to Evaluate the Efficacy and Safety of Extended Use Treatment with OncoVEX <sup>GM-CSF</sup> or GM-CSF for Eligible Melanoma Patients Participating in Study 005/05.  Andtbacka RHI, Kaufman HL, Collichio F et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33(25):2780-2788.	No
Study 002/03	OL	A Phase 2 Study of the Efficacy, Safety, and Immunogenicity of OncoVEX <sup>GM-CSF</sup> in Patients with Stage IIIC and Stage IV Malignant Melanoma.  Senzer NN, Kaufman H, Amatruda T et al. Phase II clinical trial with a second generation, GM-CSF encoding, oncolytic herpes virus in unresectable metastatic melanoma. J Clin Oncol 2009;27(15):9035.	No
Pembrolizumab			
KN-001	OL, multi-cohort	Hamid O, Robert C, Daud A et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med 2013;369:134-44.	No
KN-006	R, DB, MC	Robert C, Schachter J, Long G et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372:2521-2532.	No
Nivolumab			
CA209-066	R, DB, MC	A Phase 3, Randomized, Double-blind Study of BMS-936558 (Nivolumab) Versus Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma. 20-Oct-2014.  Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372(4):311-9.	No
Ipilimumab			
MDX010-20	R, DB, MC	A Randomized, Double-blind Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201-Positive Patients with Previously Treated Unresectable Stage III or IV Melanoma. Mar-2010.  Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010a; 363(8): 711-23.	No

Source: Table B.2-4, and Table B.2-6, p40 and p42 of the submission.

DB=double blind; MC=multicentre; R=randomised; OL=open label

- 6.6 The key features of the trials presented by the submission are summarised in Table 2. The OPTiM, CA209-066 and MDX010-20 trials were used for the informal comparison.

**Table 2: Summary of trials used in the clinical evaluation**

Trial ID	N	Trial design	Risk of bias	Primary outcome	Use in the economic evaluation
<b>T-VEC vs. GM-CSF</b>					
OPTiM	336	Phase III, R, OL, MC	High	Durable response rate	Number of injections and amount per injection
<b>Nivolumab vs. DTIC</b>					
CA209-066	411	Phase III, R, DB, MC	Low	Overall survival	Not used
<b>Ipilimumab vs. gp100</b>					
MDX010-20	676	Phase III, R, DB, MC	Low	Overall survival	Dose and number of cycles for induction and re-induction
<b>Pembrolizumab vs. ipilimumab</b>					
KN-006	834	Phase III, R, OL, MC	High	Overall survival	Not used
<b>Pembrolizumab: different doses and patient populations</b>					
KN-001	135*	Phase I, OL, multi-cohort	High	Overall response rate	Not used
<b>T-VEC: single arm</b>					
Study 002/03	50	Phase II, OL	High	Objective response rate	Not used

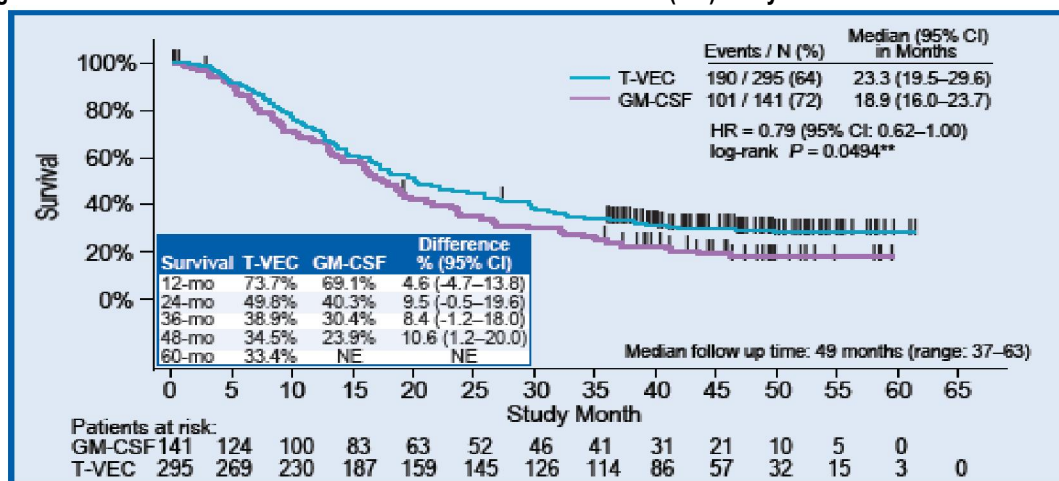
\*135 patients reported in the Hamid 2013 publication and there were 659 patients overall in the melanoma cohorts B1, B2, B3 and D of KN-001

DB=double blind; OL=open label; gp100=glycoprotein 100 peptide vaccine; DTIC=dacarbazine; T-VEC=talimogene laherparepvec; GM-CSF=granulocyte macrophage colony stimulating factor; MC=multicentre; R=randomised  
Source: compiled during the evaluation

### **Comparative effectiveness**

- 6.7 The submission stated that an indirect comparison was neither possible nor appropriate for the population of patients with stage IIIb/c and stage IVM1a melanoma, because of heterogeneity across trial populations, particularly with respect to disease stage and other prognostic factors, and the absence of comparative data in the requested PBS population.
- 6.8 The results for the secondary endpoint of overall survival (OS) for OPTiM are presented with the OS survival curves for the full cohort of patients, and a post-hoc analysis by stage of melanoma, in Figure 1 and Figure 2 respectively. These are followed by results of the informal comparison presented by the submission.

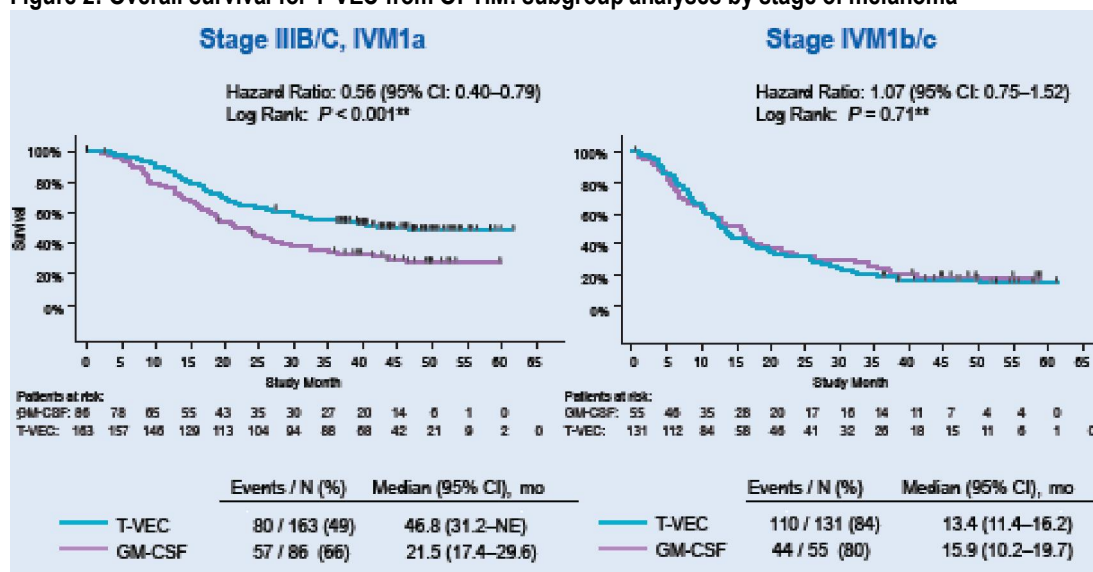
Figure 1: Overall survival for T-VEC from OPTiM: intention-to-treat (ITT) analysis



\* Planned to occur 3 years from last randomization; data cutoff Sep-05-2014. \*\*Descriptive P-value

Source: Figure B.6-1, p95 of the submission

Figure 2: Overall survival for T-VEC from OPTiM: subgroup analyses by stage of melanoma

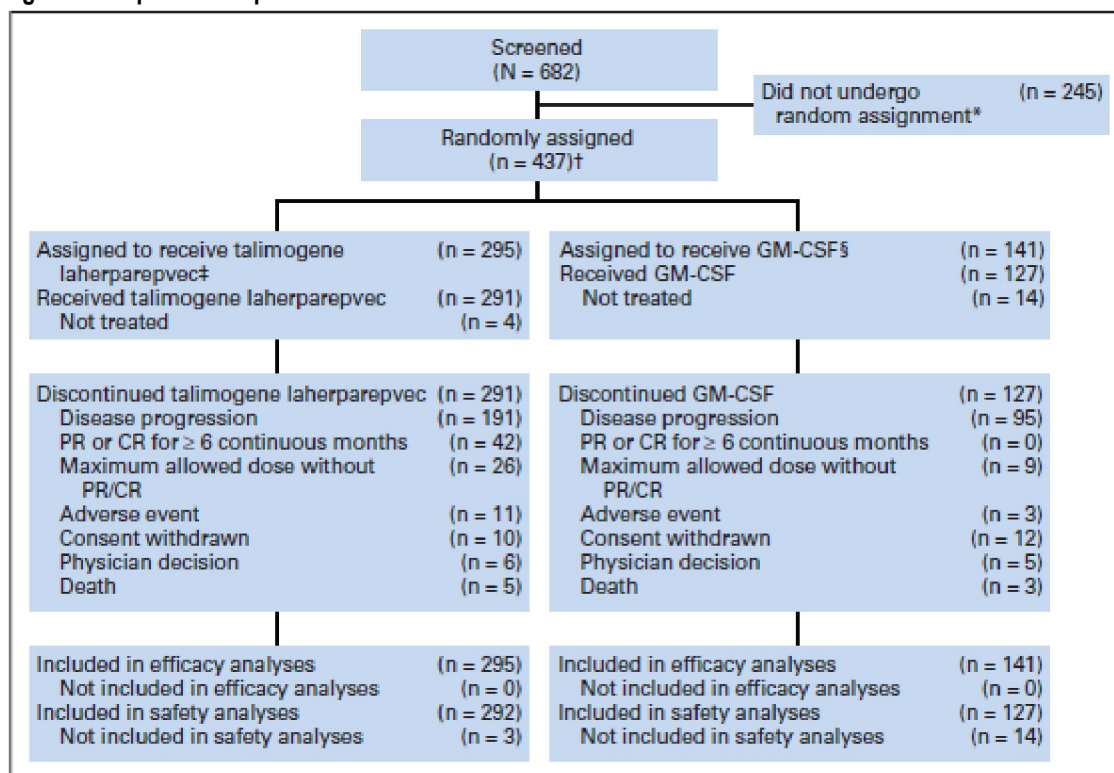


Source: Figure B.6-2, p96 of the submission

- 6.9 The results from the OPTiM trial for the entire patient population (see Figure 1) showed that any advantage for OS was on the limit of statistical significance, with an upper 95% confidence limit of 1.00. While the hazard ratio (HR) for the stage IIIB/c and stage IVM1a subgroup was lower at 0.56 (pre-specified analysis; see Figure 2), the clinical study report (CSR) for OPTiM indicated that the result for analysis by stage of treatment should be considered descriptive as it was not controlled for type 1 error. The ESC noted that OS was a secondary endpoint in OPTiM and considered that the trial was not adequately powered to demonstrate a benefit in OS.
- 6.10 The ESC noted that, in OPTiM, a greater proportion of patients assigned to receive GM-CSF were “not treated”, or discontinued due to “consent withdrawn” or “physician decision” (9.9%, 8.5% and 3.5% respectively) than in the arm assigned to receive T-VEC (1.4%, 3.4% and 2.0% respectively) (see Figure 3). This increased the risk of

attrition bias; however the direction or magnitude of this bias on the estimate of treatment effect could not be determined.

Figure 3: Disposition of patients in OPTiM



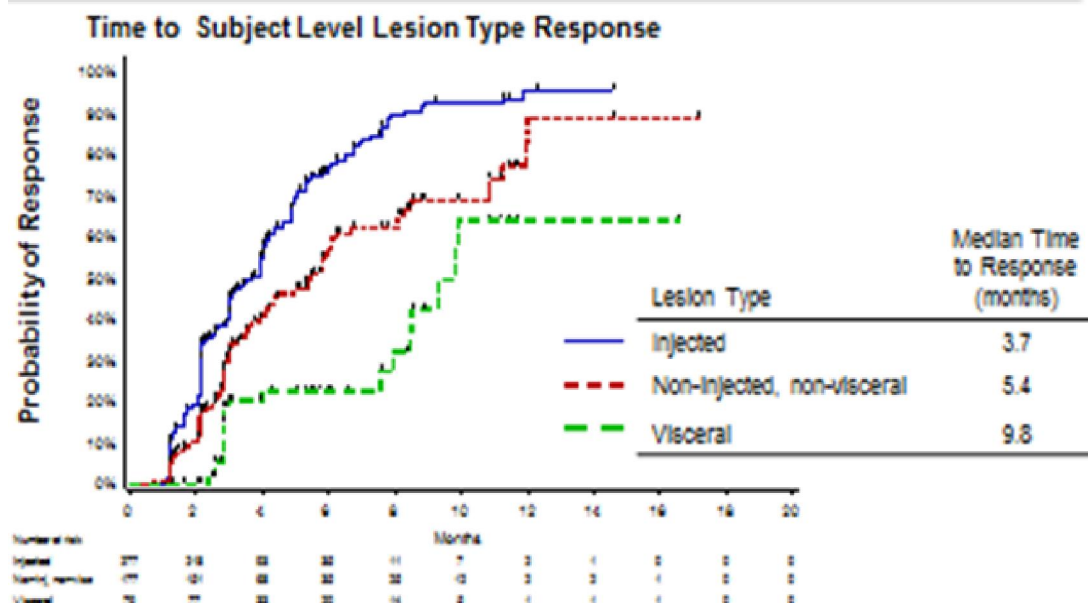
Source: Andtbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol* 2015; 33(25):2780-2788.

- 6.11 The submission assessed treatment effect variation across the two subgroups (proposed PBS population and its complementary late-stage population). The submission reported that the difference in hazard ratio for patients in the proposed PBS population compared with the remainder of patients in OPTiM was statistically significant ( $\chi^2=6.00$ ,  $df=1$ ,  $p=0.01$ ,  $I^2=83.3\%$ ), and claimed that these data demonstrated that T-VEC is beneficial in loco-regional disease, consistent with the proposed PBS listing.
- 6.12 The CSR provided a test of interaction between treatment effect and stage of disease as defined across four subgroups (stage IIIb/c, IVM1a, IVM1b and IVM1c) (p92, primary CSR). The CSR indicated this was an ad hoc analysis, but did not provide any particulars of the nature of the analysis. It was assumed to be a post-hoc analysis. The analysis returned a p-value of 0.078, which the CSR claimed suggested that the magnitude of treatment effect on OS varied among different stages of disease.
- 6.13 Based on the OPTiM trial subgroup analyses, the submission argued that directly injected and non-visceral lesions respond best to T-VEC in the stage IIIb/c and stage IVM1a population. While it could be argued that the use of T-VEC should be limited to the patient population where it is most effective, an artefact of this approach was that there is no comparable data in the same stage IIIb/c to stage IVM1a patient

population for ipilimumab, nivolumab or pembrolizumab. Consequently, no comparison of the effectiveness of T-VEC and ipilimumab could be made across the trials for the subgroup of patients proposed for the PBS listing of T-VEC. An indirect comparison of T-VEC with nivolumab or ipilimumab using the intention-to-treat (ITT) results of their key trials was also not possible, since patients enrolled in OPTiM had to have lesions that could be injected, there was no such requirement for patients in the comparator trials, and this is likely to be a treatment effect modifier for each of the compared medicines.

- 6.14 The PSCR stated that disease stage (IIIb/c, IVM1a, IVM1b, IVM1c) in OPTiM was pre-specified. The PSCR also provided data on the sub-stage effects across trials (OPTiM and Study 002/03) for response rates, and sub-stage effects for durable response rate and overall survival, and tests for interaction for covariates in OPTiM. The PSCR argued that these data support the validity of subgroup analyses and are indicative of consistently larger treatment effects in patients with earlier disease.
- 6.15 The PSCR sought to support the biological plausibility of treatment effect variation across lesion types by providing a figure which presented the results of T-VEC treatment from a source other than the OPTiM trials (see Figure 4).

Figure 4: Figure 1 from p6 of PSCR



- 6.16 The ESC noted that, from the ITT population of OPTiM, the median time to response among the 78 responding patients in the T-VEC arm was 4.1 months, with a range between 1.2 to 16.7 months. These results were not broken down by lesion type, but are broadly consistent with the results presented in Figure 1 from the PSCR. The ESC considered that the apparent delay of responses in visceral lesions to beyond 6 months did not suggest an obvious treatment effect by T-VEC on visceral lesions, supporting the acceptance of the sub-group analysis focusing on patients with Stage IIIb/c and IVM1a melanoma.

- 6.17 The submission then presented an informal comparison of hazard ratios for comparisons of T-VEC, ipilimumab and nivolumab to an ineffective control, based on the results of OS from the stage IIIb/c to stage IVM1a patients in OPTiM for T-VEC, and the entire population of patients in MDX010-20 for ipilimumab and CA209-066 for nivolumab. Results for the comparison of T-VEC to pembrolizumab were not presented since a hazard ratio against an “ineffective control” was not reported in the trials. Table 3 provides the results of the informal comparison of T-VEC and nivolumab and T-VEC and ipilimumab, for overall survival. Since the primary outcome of durable response rate in OPTiM for T-VEC was not an outcome in the other trials, and since OPTiM did not report on progression free survival, OS provided the most appropriate outcome for comparison across the trials.

**Table 3: Informal comparison of OS for T-VEC and nivolumab, and T-VEC and ipilimumab**

<b>Trial</b>	<b>Active therapy</b>	<b>Comparator</b>	<b>HR (95%CI)</b>
<b>OPTiM – T-VEC</b>	<b>T-VEC n/N (%)</b>	<b>GM-CSF n/N (%)</b>	
Death (ITT)	190/295 (64%)	101/141 (72%)	0.79 (0.62, 1.00)
OS median (95% CI), months	23.3 (19.5, 29.6)	18.9 (16.0, 23.7)	-
Death (stage IIIb/c, IVM1a subgroup)	80/163 (49%)	57/86 (66%)	0.56 (0.40, 0.79)**
OS median (95% CI), months	46.8 (31.0, NE)	21.5 (17.4, 29.6)	-
<b>CA209-066* – nivo</b>	<b>Nivo n/N (%)</b>	<b>DTIC n/N (%)</b>	
Death	50/210 (24%)	96/208 (46.2%)	0.42 (0.30, 0.59)
OS median (95% CI), months	Not reached	10.8 (9.3, 12.1)	-
<b>MDX010-20 – ipi</b>	<b>Ipi n/N (%)</b>	<b>gp100 n/N (%)</b>	
Death	100/137 (73%)	119/136 (88%)	0.64 (0.49, 0.84)
OS median (95% CI), months	10.1 (8.0, 13.8)	6.4 (5.5, 8.7)	-

T-VEC=talimogene laherparepvec; DTIC=dacarbazine; HR=hazard ratio; Ipi=ipilimumab; Nivo=nivolumab; OS=overall survival

\*Updated 2-year OS rates based on at least 15.1 months of follow-up from <http://global.onclive.com/conference-coverage/smr-2015/nivolumab-survival-benefit-sustained-in-long-term-melanoma-data> indicate that median OS had not been reached at 2 years with 57.7% of nivolumab patients and 26.7% of DTIC patients alive at 2 years (HR=0.43 [0.33,0.57])

\*\*Based on values cited in Figure 2

Source: Table B.6-3 and Table B.6-4, p94 and p104-105 of the submission and Figures B.6-1 and B.6-2, p95-96 of the submission

- 6.18 No statistical comparisons of the data were provided. The informal comparisons did not provide any reliable information for decision-making on the comparative efficacy of T-VEC to nivolumab, ipilimumab, or pembrolizumab, particularly given that the median duration of follow-up differed considerably across the trials (16 months for CA209-066, 44 months for OPTiM and 55 months for MDX010-20); and the populations in each trial were not comparable.
- 6.19 The ESC noted from the PSCR that there is unlikely to be any direct evidence comparing T-VEC monotherapy with an appropriate monotherapy comparator, as current on-going trials are investigating T-VEC in combination with active therapies, such as pembrolizumab and ipilimumab. The ESC therefore advised that the proposed clinical place for T-VEC monotherapy in treatment of metastatic melanoma was difficult to justify in the current disease setting, where systemic agents are available to treat both localised lesions and metastases. The ESC expressed concern for potential early metastases that are not detected (clinical or ultrasound) at the time of patient treatment with T-VEC, which may delay necessary systemic therapy with other agents. The ESC suggested that there might potentially be a place for T-VEC in the future as an add-on therapy for the management of resistant lesions.

### **Comparative harms**

- 6.20 The submission presented only a naïve comparison of safety outcomes and claimed that the safety of T-VEC is similar to nivolumab and pembrolizumab and more favourable than that of ipilimumab. The most common adverse events in OPTiM were chills, pyrexia, influenza-like illness, injection site reactions and cellulitis. Immune-related adverse events were more common with the other treatments, particularly ipilimumab. As the submission did not provide either an indirect or a statistical comparison of T-VEC to either pembrolizumab, nivolumab or ipilimumab, it was not possible to ascertain whether the adverse event profile of T-VEC is different to that of these other treatments. It is however clear that there is a risk of herpetic infection with T-VEC, and that precautions need to be taken to avoid accidental exposure. Overall, the evidence presented by the submission did not allow any conclusion to be drawn on comparative safety.

### **Clinical claim**

- 6.21 Based on restricting the use of T-VEC to patients with stage IIIb/c or stage IVM1a malignant melanoma, the submission described T-VEC as:
- similar in terms of comparative efficacy to ipilimumab, pembrolizumab, and nivolumab;
  - similar in terms of terms of comparative safety to pembrolizumab and nivolumab; and
  - having a favourable safety profile compared to ipilimumab.
- 6.22 The submission's claims were not adequately supported. Given that the submission did not present statistical comparisons and that the trial populations were considerably different, it was not possible to form any view on the comparative efficacy or safety of T-VEC compared to pembrolizumab, nivolumab or ipilimumab from the data presented.
- 6.23 The PBAC considered that the claims of non-inferior comparative effectiveness and non-inferior comparative safety were not adequately supported by the data provided. Given that only an informal comparison of T-VEC with its nominated comparators was conducted, comparative efficacy and safety could not be determined.

### **Economic analysis**

- 6.24 The submission presented a cost-minimisation analysis of T-VEC compared to ipilimumab using the full published price for ipilimumab and the proposed published price for T-VEC. The submission anticipated that the effective T-VEC price would be agreed upon if there was a positive PBAC recommendation, with the submission proposing to negotiate an effective price for T-VEC based on cost-minimisation to match the effective price of ipilimumab. As the non-statistical informal comparison presented by the submission did not establish whether T-VEC is inferior or non-inferior to the comparator, there was no evidentiary basis for a cost-minimisation analysis. Nonetheless, the claimed equi-effective doses and the cost-minimisation analysis provided by the submission are presented below.
- 6.25 The claimed equi-effective doses were estimated as T-VEC 1 mL and ipilimumab 5.78 mL. Details of the calculations are shown in Table 4.

**Table 4: Calculation of equi-effective dose for T-VEC compared to ipilimumab**

Parameter	Source	Number of vials and doses	Total dose per patient lifetime	Dose relativity
<b>T-VEC</b>				
Doses per patient	OPTiM: mean injections per patient*	1 dose of 1 million PFU/mL and [REDACTED] doses of 100 million PFU/mL	[REDACTED] mL	[REDACTED] mL
Vials per admin	OPTiM: not including rounding up to whole vials to account for wastage**	[REDACTED] × 1 mL of 1 million PFU/mL and [REDACTED] × 1 mL of 100 million PFU/mL		
<b>Ipilimumab</b>				
Doses per patient	MDX010-20	3.73 doses	964.73 mg (192.95 mL)	[REDACTED] mL
Vials per admin	Based on patient weight of: 86.13 kg from MDX010-20 and 3 mg/kg	50 mg/10 mL: 1.35 vials; 200 mg/40 mL: 1.01 vials (= 258.4 mg)		

\* Based on the mean dose of T-VEC from the stage IIIb/c and stage IVM1a subgroup, excluding doses given as accelerated doses, excluding doses given during the extension phase of the trial, and there was an assumption that the proposed PBS continuation rules for PR, CR or SD at 6 months would apply.

\*\*While the dose relativity calculation does not include wastage, wastage is accounted for in the cost-minimisation analysis.

PFU=plaque forming units; T-VEC=talimogene laherparepvec

Source: compiled during the evaluation

- 6.26 The dose relativity was calculated based on mean total drug use over a patient lifetime for T-VEC and ipilimumab based on the doses and cycles and patient weight for T-VEC in OPTiM and ipilimumab in MDX010-20.
- 6.27 Given the truncated follow-up of the OPTiM trial, the duration of therapy with T-VEC may be greater than that reported in OPTiM (i.e. without any extrapolation beyond the trial horizon), increasing the mean number of mg of T-VEC used per patient lifetime. In contrast, use of ipilimumab in clinical practice is lower than that reported in MDX010-20. An alternate calculation of the “equi-effective” doses conducted during the evaluation, using the actual unadjusted mean trial based usage of T-VEC of [REDACTED] injections and the mean number of cycles of ipilimumab derived from the submission’s 10% PBS sample of 3.18 (and also noting that there are no outcomes data associated with PBS data at all), resulted in a dose relativity of [REDACTED] mL of T-VEC = 820 mg of ipilimumab (164 mL): T-VEC [REDACTED] mL = ipilimumab [REDACTED] mL.
- 6.28 The cost-minimisation analysis presented by the submission is shown in Table 5. While the calculation of equi-effective doses did not account for wastage, the cost-minimisation analysis included wastage costs for T-VEC, by applying the T-VEC vial price to the mean number of whole vials per injection day rather than to the number of whole vials required to deliver the mean dose. This was appropriate.
- 6.29 The submission did not include any difference in the cost of adverse events for T-VEC or for the comparators in the cost-minimisation analysis. As the submission did not provide any statistical evidence that adverse events were the same or whether they differed between the therapies, it is not possible to determine whether cost differences due to adverse events should have been included.

**Table 5: Cost-minimisation analysis**

	T-VEC**	Ipilimumab*	Difference
Mean total vials	[REDACTED] × 1 million PFU/mL, 1 mL	3.77 × 40 mL	-

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	33.61 x 100 million PFU/mL, 1 mL	5.04 x 10 mL	
Mean drug cost***	\$119,886	\$120,644	-\$759
Total administration cost	\$1,238	\$366	\$872
Total cost	\$121,123	\$121,010	\$113

\*Based on fee for MBS item 14245 of \$97.95 x 3.73 cycles

\*\*Based on fees for MBS items 30207 of \$44.60 and 105 of \$43 x [redacted] injections

\*\*\*Refer to Table 6

The total cost of T-VEC and ipilimumab were modified during the evaluation to take into account a preparation fee of \$102.67 rather than the \$82.67 used by the submission

PFU=plaque forming units; T-VEC = talimogene laherparepvec

Source: Table D.2-5, p136 of the submission

- 6.30 Based on administration costs of \$87.60 for T-VEC and \$97.95 for ipilimumab, and no difference in costs for adverse events, and the submission's estimates for dose and number of doses of ipilimumab and T-VEC per patient lifetime (adjusted for the \$102.67 preparation fee instead of an \$82.67 preparation fee), there was a net difference of \$113 per patient lifetime for the use of T-VEC compared to ipilimumab. As the submission did not include the cost of ultrasound guidance, which may be required for T-VEC, or the cost of preventing herpetic spread, the total cost of using T-VEC was considered to be underestimated.
- 6.31 The PSCR provided proportions of patients who may require ultrasound guidance, based on the T-VEC arm of the OPTiM trial (Table 6). The ESC noted that the need for ultrasound guidance may potentially be close to half of patient cases (48%) with certain lesion types.

**Table 6: Location of lesions in patients in T-VEC arm by measurement modality**

Injected lesions type	N = 291, n (%)	Measurement modality, n (%)	
		Clinical	Ultrasound guidance
Cutaneous or subcutaneous lesion only	179 (61.5%)	Clinical	169 (94)
		Ultrasound guidance	20 (11)
Nodal lesions only	36 (12.4%)	Clinical	21 (58)
		Ultrasound guidance	13 (36)
Cutaneous/subcutaneous and nodal	67 (23%)	Clinical	56 (84)
		Ultrasound guidance	32 (48)

**Drug cost/patient/lifetime: \$119,886.**

- 6.32 The cost of T-VEC per patient lifetime was calculated to be \$119,886. Details of the calculations are shown in Table 7.

**Table 7: Summary of drug costs/patient/lifetime for T-VEC and ipilimumab**

Parameter	Source	Number of vials and doses	Drug cost/admin	Drug cost/patient/lifetime
<b>T-VEC</b>				
Doses per patient	OPTiM: mean injections per patient	█ dose of 1 million PFU/mL and █ doses of 100 million PFU/mL (14.13 doses in total)	\$8,484.50*	\$119,886
Vials per admin	OPTiM: including rounding up to whole vials to account for wastage	█ × 1 mL of 1 million PFU/mL and █ × 1 mL of 100 million PFU/mL		
<b>Ipilimumab</b>				
Doses per patient	MDX010-20	3.73 doses	\$32,313.06	\$120,644
Vials per admin	Based on patient weight of: 86.13 kg from MDX010-20 and 3 mg/kg	258.4 mg per dose 50 mg/10 mL: 1.35 vials; 200 mg/40 mL: 1.01 vials		

These costs include a preparation fee of \$102.67 rather than the \$82.67 that is assumed to be the preparation fee by the submission.

The costs assume a 40/60 public/private split of prescriptions

\*Assuming a weighted DPMA of \$█ per 1mL vial for T-VEC (the weighted DPMA used in the submission after adjustment for the \$102.67 preparation fee instead of the \$82.67 used by the submission).

PFU=plaque forming units; T-VEC=talimogene laherparepvec

Source: compiled during the evaluation

- 6.33 The cost of T-VEC per patient lifetime was calculated based on the mean number of vials per injection used in OPTiM and the mean number of injections per patient, excluding accelerated dosing, excluding patients who entered the extension phase of the trial, and assuming that the proposed PBS continuation rules for partial response (PR), complete response (CR) or stable disease (SD) at 6 months would apply. This equated to █ mL of T-VEC per patient lifetime (█ mL of 1 million PFU/mL and █ injections of █ mL of 100 million PFU/mL), noting that there are minor differences in the drug cost/patient/lifetime due to rounding.
- 6.34 There was no allowance for re-treatment with T-VEC in the future should new lesions develop. In clinical practice, patients may remain on therapy with T-VEC for longer than assumed by the submission. As such, the cost per patient lifetime is considered to be underestimated. The PSCR stated that the Sponsor does not intend to allow re-treatment with T-VEC in patients in whom new lesions arise, on the basis that there is no evidence for retreatment. The ESC considered that re-treatment of new lesions would be theoretically beneficial and patients could potentially have multiple episodes of re-treatment. Given that the median time to response ranged from 1.2 to 16.7 months in OPTiM, there is the potential that some patients may receive a longer duration of treatment.

**Estimated PBS usage & financial implications**

- 6.35 This submission was not considered by DUSC. The submission used a combined epidemiological/market share approach to estimate the extent of use and financial implications of listing T-VEC for the treatment of unresectable malignant melanoma without visceral metastases.
- 6.36 The submission used the cost per patient to the PBS of ipilimumab as a proxy for the corresponding costs of pembrolizumab and nivolumab, since the submission stated

that this cost of ipilimumab with its fixed number of treatment cycles could be calculated more reliably than for pembrolizumab or nivolumab, which are given until disease progression. The submission used the published price of ipilimumab in estimating the financial impact of listing T-VEC on the PBS. This approach was reasonable since the submission proposed a reduced effective price for T-VEC to match the effective price of ipilimumab.

- 6.37 The estimated use and financial implications of listing T-VEC on the PBS are shown in Table 8.

**Table 8: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
T-VEC treated patients*					
Total number of 1 mL vials**					
T-VEC cost	\$	\$	\$	\$	\$
Cost of substituted therapies	\$	\$	\$	\$	\$
Net cost to the PBS/RPBS	-\$	-\$	-\$	-\$	-\$
Net administration costs	\$	\$	\$	\$	\$
<b>Net cost to health budget</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>

\*An uptake rate of 5% in year 1 increasing to 20% in year 5 was assumed for *BRAF* wild-type patients, and 3% in year 1 increasing to 10% in year 5 for patients with the *BRAF* mutation

\*\* Assuming one script for 2.86 vials of 1 million PFU/mL and 13.13 scripts for 2.56 vials of 100 million PFU/mL of T-VEC per patient

PFU=plaque forming units; T-VEC=talimogene laherparepvec

Source: Table E.2.2-1, p150, Table E.4.1-1, p152, Tables E.5.1 to E.5.-3, p152-154 of the submission

The redacted table shows that at year 5, the estimated number of T-VEC treated patients would be less than 10,000 per year and the net saving to the PBS would be less than \$10 million per year.

- 6.38 Patient numbers were considered to be substantially underestimated as a result of underestimation of the growth rate of the market, failure to consider prevalent patients, and underestimation of the uptake rate.
- 6.39 While the submission accounted for wastage of T-VEC by rounding up the dose to the next whole number of vials required, the mean number of injections per patient lifetime was considered to be underestimated. The submission excluded the doses given to patients in the extension phase of the trial as well as doses given to patients who had progressive disease after 6 months. If T-VEC is listed on the PBS, despite a requirement for CR, PR or SD for continued use, use may still occur in patients with progressive disease after this 6-month time point. In addition, there was an artificial treatment cut-off point for patients as a result of the trial environment. In practice, patients may still have lesions that can be injected for substantially longer than the 18-month duration of the OPTiM trial (non-extension phase), as well as new lesions that may develop. Consequently, as the mean duration of treatment with T-VEC in clinical practice is likely to be longer than that assumed for the financial estimates, the total cost of T-VEC to the PBS may be more than estimated in the submission. The sponsor has signalled a willingness to enter into discussion around a risk share arrangement to address uncertainty surrounding the number of vials of T-VEC required per patient lifetime.
- 6.40 The submission estimated that, should T-VEC be listed in the PBS, the number of patients that would be treated with T-VEC would be equal to the same number of

patients who would no longer be treated with its comparators. It is more likely that there will be some displacement of the comparators into later lines of therapy, and therefore the submission's estimate of reduced costs to the PBS are considered to be overestimated. The ESC reiterated that the nominated comparators would still likely be used following treatment with T-VEC, or possibly in combination with T-VEC outside the intention of the requested restriction for T-VEC.

- 6.41 As in its economic evaluation, the submission did not include any difference in the cost of adverse events for T-VEC or for its comparators in the financial analyses.
- 6.42 The submission assumed that the net cost to the MBS would be limited to the cost of administration, with the cost to administer T-VEC being 85% of the fee for MBS30207 (the code for multiple injections of hydrocortisone, or similar preparations) and MBS105 for a specialist consultation. The cost to administer T-VEC is unclear. There is the need for ultrasound guidance in some cases, and with measures required to prevent herpetic spread, the cost of administration may be higher than estimated in the submission. There is also a cost to store T-VEC appropriately at -90 to -70 degrees Celsius; however this cost is likely to be incurred outside the PBS and the MBS.
- 6.43 Sensitivity analyses indicated the financial estimates were most sensitive to the number of vials of T-VEC used per patient.

#### **Quality Use of Medicines**

- 6.44 The submission proposed a number of activities to support the quality use of medicines, including education by the sponsor for health care professionals to ensure appropriate handling of T-VEC and care of injection sites and for patients to prevent of inadvertent transfer of the virus.

#### **Financial Management – Risk Sharing Arrangements**

- 6.45 The sponsor indicated a willingness to undertake a risk sharing arrangement to account for the uncertainty surrounding the average number of vials of T-VEC that will be used in clinical practice. The submission did not provide any details of the potential risk sharing arrangement.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the listing of T-VEC on the basis of highly uncertain magnitude of clinical benefit, and thus highly uncertain cost effectiveness compared to its nominated comparators (pembrolizumab, nivolumab and ipilimumab).
- 7.2 The PBAC acknowledged that there may be some short-term unmet clinical need for additional therapies beyond current PBS-subsidised medicines in a small subgroup of previously untreated patients with stage IIIb/c and stage IVM1a melanoma. The PBAC also noted that current clinical trials were evaluating the role of T-VEC as an add-on therapy to current PBS-subsidised medicines.

- 7.3 The PBAC accepted that pembrolizumab, nivolumab and ipilimumab were appropriate comparators. The PBAC considered that BRAF/MEK inhibitors (such as dabrafenib with trametinib), and intra-lesional BCG, were also relevant comparators, however noted that the latter was not PBS-subsidised.
- 7.4 The PBAC considered that intra-lesional T-VEC was likely to displace, rather than replace, its comparators. It may also be used as concomitant therapy, whether added to other non-PBS-subsidised therapies, or used beyond the requested restriction with its comparators.
- 7.5 The PBAC considered that durable response rate, the primary endpoint in the key trial (OPTiM), was not a validated endpoint, as it was clinician assessed, and allowed patients to be counted as having durable response despite having disease relapse or disease progression after 6 months. There was no quality-of-life data reported from this trial in the submission. The PBAC considered that the magnitude of survival benefit of T-VEC in the stage IIIb/c and stage IVM1a subgroups was highly uncertain, given the data was derived from an exploratory post-hoc subgroup analysis of a secondary endpoint of the OPTiM trial, and that the survival benefit in the whole population was of borderline statistical significance.
- 7.6 The PBAC considered that the comparative effectiveness and safety of T-VEC versus its comparators could not be determined with sufficient confidence using the data presented in the submission. The PBAC noted that the available trials differed markedly in their comparators, participant eligibility, baseline disease characteristics, trial outcomes and length of follow-up. As each of these differences is likely to modify the comparative treatment effects of T-VEC, pembrolizumab, nivolumab and ipilimumab against their comparators (with particular emphasis on the effect of T-VEC being modified by the staging of melanoma despite some evidence of an attrition bias), the assumption of transitivity across these effects was unlikely to hold, and thus any indirect comparison of T-VEC and its comparators could not be relied upon. The PBAC also noted the lack of a formal statistical indirect comparison between T-VEC and its comparators. Therefore, there was also inadequate basis for the cost-minimisation analysis of T-VEC versus ipilimumab at its effective price, as the submission did not establish whether T-VEC was inferior or non-inferior to any of its comparators.
- 7.7 The PBAC noted that the estimates of the comparative treatment effects (for example, on durable response rates or overall survival) may be subject to bias due to differences across trials which result in effect modification. The trials forming a “transitivity analysis” to estimate the comparison of these effects may differ in comparators, participant eligibility, baseline participant and disease characteristics, trial outcomes, length of follow-up, and other unknown factors. These differences in the trials may not be known and where known may not be reported. However, they confound the results of the common reference which forms the “anchor treatment” of the transitivity analysis, to the extent that (a) they modify the comparative treatment effect, and (b) their distributions vary across the identified trials. In so doing, they generate a treatment by trial interaction. The PBAC noted that this emphasis on assessing the assumption of “transitivity” is narrower than assessing the assumption of “exchangeability” (which had followed the work of the Indirect Comparisons Working Group), because it focusses on those differences across trials which are

expected to vary the comparative treatment effect.

- 7.8 The PBAC noted that the submission assumed no difference in the costs of managing potential adverse events, and did not include costs of T-VEC administration beyond a simple injection, such as ultrasound guidance and precautions to prevent herpetic spread. The PBAC considered that the exclusion of these potential costs from the economic evaluation was inappropriate. The likely underestimation of costs associated with T-VEC contributed to PBAC's concern that the cost-effectiveness of T-VEC was highly uncertain.
- 7.9 The PBAC considered that the total financial impact was uncertain and likely underestimated, given the assumed low uptake and market growth rate of T-VEC and uncertain number of T-VEC vials used per patient lifetime.
- 7.10 The PBAC advised that, for any future resubmission, any indirect comparison of T-VEC versus its nominated comparator(s) would require cross-trial indirect statistical comparisons of both the specified subgroups and the whole population in order to better inform some of the treatment effect modifiers affecting the transitivity assumption and thus appropriate adjustment of the analyses. Any economic evaluation would need to justify the comparative costs of T-VEC against its comparators, including by adequately accounting for potential adverse events and the full costs of T-VEC administration. The PBAC also considered that a financial cap would be required given the uncertainty of treatment duration with T-VEC; treatment may need to be restricted to patients with a performance status  $\leq 1$ ; and any PBS listing would require a continuation restriction. Alternatively, the PBAC suggested that the sponsor may wish to compare T-VEC with other intra-lesional therapy such as BCG. The latter approach would offer the opportunity to compare products with similar manners of administration in trials with likely more similar patient populations, and possibly more similar common references and trial outcomes. However, this approach would also require some basis for considering the cost-effectiveness of BCG.
- 7.11 The PBAC noted that current trials of T-VEC as an add-on therapy is underway, and expressed interest for a major submission of T-VEC as an add-on therapy if positive clinical trial results become available and an application to TGA in this setting is underway.
- 7.12 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

Despite a number of promising melanoma therapies recently being recommended by the PBAC, Australia still has one of the highest incidences of melanoma in the world and there remains a clinical need for alternative treatment options. Talimogene laherparepvec (IMLYGIC) is effective and well tolerated while offering a new and different mode of action that provides a useful addition to existing therapies. Amgen looks forward to continuing to work with the PBAC to ensure that Australian patients with melanoma are able to access treatment with talimogene laherparepvec.