NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talimogene laherparepvec for treating metastatic melanoma

Patient access scheme submission template

January 2016

File name	Version	Contains confidential information	Date
		Yes CIC: Highlighted in turquoise and underlined	January 2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: Talimogene laherparepvec (brand name: Imlygic)

Disease area: Unresectable metastatic melanoma; talimogene laherparepvec is indicated "for the treatment of adults with unresectable melanoma that regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease"

3.2 Please outline the rationale for developing the patient access scheme.

The rationale behind the patient access scheme is to provide talimogene laherparepvec at a cost-effective price to the NHS, mitigating any risk to the NHS due to limitations of the evidence base of ipilimumab and other comparator treatments in the licensed population for talimogene laherparepvec.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The proposed patient access scheme is a simple scheme (confidential discount off the NHS list price of the10^6pfu/mL x1mL and 10^8pfu/mL x1mL vials of talimogene laherparepvec). The proposed confidential discount is [redacted]. The scheme is expected to be implemented at the time of positive NICE guidance, expected in July 2016.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme applies to the whole population for which talimogene laherparepvec is licensed, i.e. for adults with unresectable melanoma that regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any additional criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Not applicable.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The price (including the patient access scheme confidential discount) will be demonstrated to NHS organisations on the original invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See above.

3.10 Please provide details of the duration of the scheme.

The patient access scheme will remain in place until NICE next reviews the product under the technology appraisals programme and a final decision has been published by NICE (as per the declaration signed by Amgen in the patient access scheme proposal template).

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The patient access scheme does not require any additional forms, registration or other administrative process to claim the discount.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The patient access scheme applies to the entire licensed population for talimogene laherparepvec – the population presented in the main submission of evidence.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Patient access scheme is likely to be approved prior to the first Appraisal Committee meeting. No changes have been made to the model.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The patient access scheme has been incorporated into the economic model by utilising the discounted price per vial for talimogene laherparepvec that would apply in the context of a simple discount. The NHS list price of talimogene laherparepvec is £1,670 per vial (10^6pfu/mL x1mL and 10^8pfu/mL

x1mL vials). It is noteworthy that the anticipated NHS list price for talimogene laherparepvec in the manufacturer submission has been updated and no longer holds and the final NHS list price is £1,670 (confirmed with the Department of Health). The patient access scheme is a fixed price of [redacted] per vial (10^6pfu/mL x1mL and 10^8pfu/mL x1mL vials). The patient access scheme (talimogene laherparepvec drug cost) has been implemented in the economic model in the 'Drug Costs' worksheet and descriptively in the 'Drug Cost Calcs' worksheet.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data for talimogene laherparepvec from the pivotal OPTiM trial is presented in Table 1. This data underpins the economic model in the evidence submission and remains the same regardless of the implementation of the patient access scheme.

Table 1: Key outcomes from the OPTiM trial (Stage IIIB, IIIC and IVM1a with no bone, brain, lung or other visceral disease population)

Talimogene laherparepvec (OPTiM) Final descriptive data cut 8th August 2014		
Outcome	**T-VEC (N = 163)**	**GM-CSF (N = 86)**
Median OS months (95% CI)	46.8 (31.2, NE)	21.5 (17.4, 29.6)
HR (95% CI); p-value	0.56 (0.40, 0.79); p=0.0008	
Median PFS (months) (95% CI)	13.1 (8.3, NE)	3.3 (2.8, 4.3)
HR (95% CI); p-value	0.27 (0.19, 0.39); p=<0.0001	
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival (Time to treatment failure [TTF] used as proxy); NE, not estimable; T-VEC, talimogene laherparepvec.		

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There will be no costs associated with the implementation and operation of the proposed patient access scheme as this scheme involves a simple confidential discount of [redacted] applied at the point of order.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of the patient access scheme will not incur additional treatment-related costs.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Our manufacturer's evidence submission presents the cost-effectiveness results for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

anticipated NHS list price for talimogene laherparepvec no longer holds and the final NHS list price is £1,670. The results using the final NHS list price are presented in Table 2 below. The cost-effectiveness results including the proposed patient access scheme for talimogene laherparepvec are presented in Table 3.

Table 2 Base-case cost-effectiveness results (NHS list price [without PAS])

	Ipilimumab	Talimogene laherparepvec
Modified Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£28,752	£35,561
Adverse event costs	£118	£3
Total costs	£98,219	[redacted]
Difference in total costs	NA	[redacted]
LYG	4.90	6.66
LYG difference	NA	1.76
QALYs	3.57	4.91
QALY difference	NA	1.34
ICER (£ per QALY gained)	NA	[redacted]
Two-step Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£26,567	£34,419
Adverse event costs	£118	£3
Total costs	£96,035	[redacted]
Difference in total costs	NA	[redacted]
LYG	6.16	6.66
LYG difference	NA	0.50
QALYs	4.61	4.95
QALY difference	NA	0.35
ICER (£ per QALY gained)	NA	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable.

Table 3 Base-case cost-effectiveness results (with PAS)

	Ipilimumab	Talimogene laherparepvec
Modified Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£28,752	£35,561
Adverse event costs	£118	£3
Total costs	£98,219	[redacted]
Difference in total costs	NA	[redacted]
LYG	4.90	6.66
LYG difference	NA	1.76
QALYs	3.57	4.91
QALY difference	NA	1.34
ICER	NA	-£16,367
Two-step Korn		
Intervention cost	£68,038	[redacted]
Administration costs	£1,311	£5,092
Resource use cost	£26,567	£34,419
Adverse event costs	£118	£3
Total costs	£96,035	[redacted]
Difference in total costs	NA	[redacted]
LYG	6.16	6.66
LYG difference	NA	0.50
QALYs	4.61	4.95
QALY difference	NA	0.35
ICER (£ per QALY gained)	NA	-£60,271

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable; PAS, patient access scheme.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 4 Base-case incremental results (NHS list price [without PAS])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Modified Korn							
Ipilimumab	[redacted]	4.90	3.57	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.91	[redacted]	1.76	1.34	[redacted]
Two-Step Korn							
Ipilimumab	[redacted]	6.16	4.61	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.95	[redacted]	0.50	0.35	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable.

Table 5 Base-case incremental results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Modified Korn							
Ipilimumab	[redacted]	4.90	3.57	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.91	[redacted]	1.76	1.34	-£16,367
Two-Step Korn							
Ipilimumab	[redacted]	6.16	4.61	NA	NA	NA	NA
Talimogene laherparepvec	[redacted]	6.66	4.95	[redacted]	0.50	0.35	-£60,271

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NA, not applicable; PAS, patient access scheme.

Ipilimumab is available with an approved PAS (simple confidential discount) to the NHS. Given the confidential nature of the PAS, a comparison of the ICERs using a range of simple discounts (from 0%-100%) to reflect the possible PAS price for ipilimumab is presented in Table 6 below. It should be noted that these results are based on the PAS price for talimogene laherparepvec.

Table 6 Comparison of ICERs assuming a range of potential discounts for ipilimumab with PAS price for talimogene laherparepvec

Potential discounts for ipilimumab	Modified Korn	Two-Step Korn
	£/QALY	£/QALY
0%	[redacted]	[redacted]
5%	[redacted]	[redacted]
10%	[redacted]	[redacted]
15%	[redacted]	[redacted]
20%	[redacted]	[redacted]
25%	[redacted]	[redacted]
30%	[redacted]	[redacted]
35%	[redacted]	[redacted]
40%	[redacted]	[redacted]
45%	[redacted]	[redacted]
50%	[redacted]	[redacted]
55%	[redacted]	[redacted]
60%	[redacted]	[redacted]
65%	[redacted]	[redacted]
70%	[redacted]	[redacted]
75%	[redacted]	[redacted]
80%	[redacted]	[redacted]
85%	[redacted]	[redacted]
90%	[redacted]	[redacted]
95%	[redacted]	[redacted]
100%	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Our manufacturer's evidence submission presents the results of the deterministic sensitivity analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The anticipated list price for talimogene laherparepvec is no longer valid and Figure 1 below presents results using the final NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results including the proposed patient access scheme for talimogene laherparepvec are presented in Figure 2.

Figure 1 Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, with NHS list prices for talimogene laherparepvec and ipilimumab)

a. **Using Modified Korn Adjustment**

[redacted]

T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

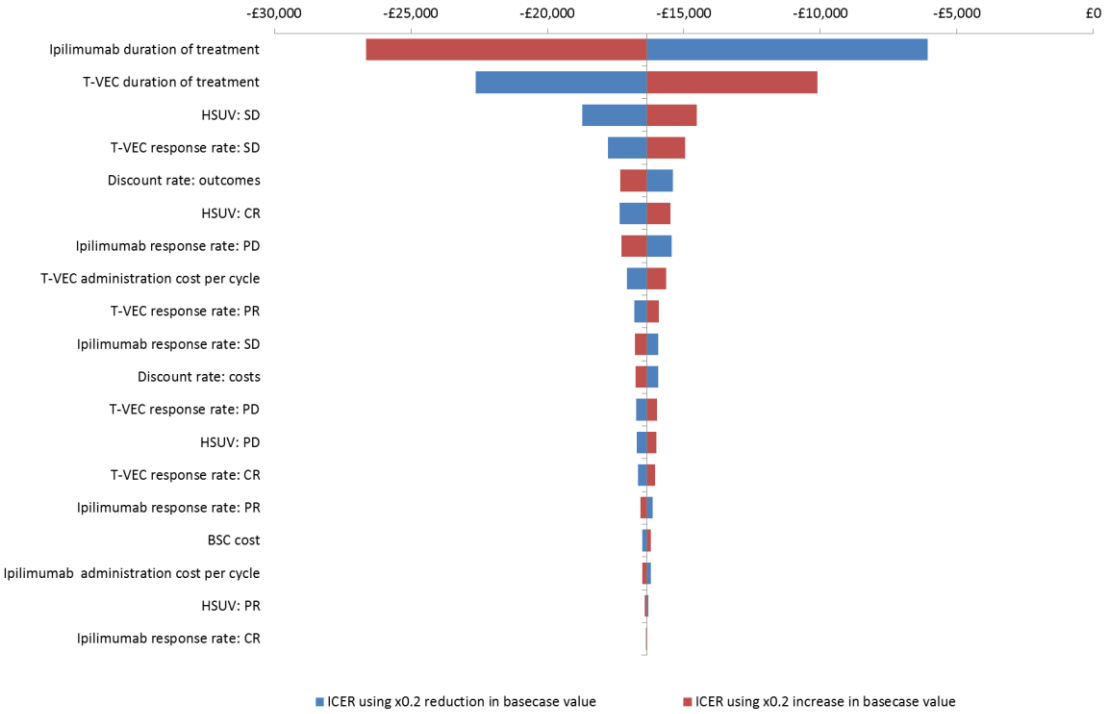
b. Using Two-Step Korn Adjustment

[redacted]

T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

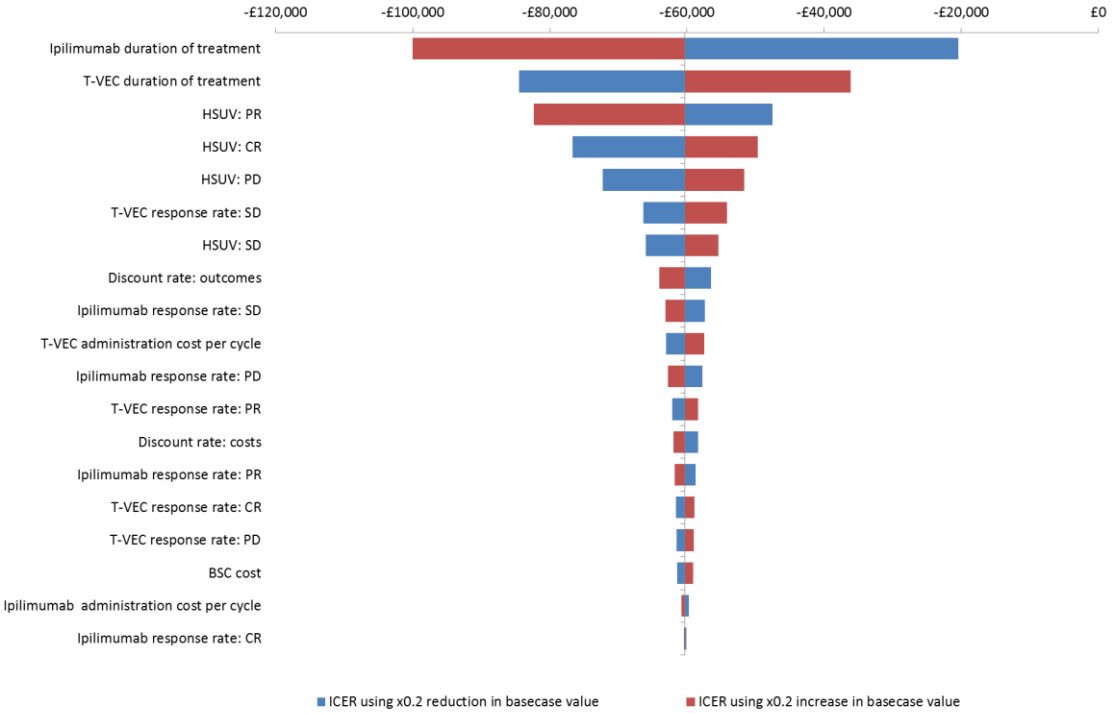
Figure 2 Tornado diagram presenting the results of the deterministic sensitivity analysis versus ipilimumab for the most sensitive variables (discounted results, including the patient access scheme for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR: partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

b. Using Two-Step Korn Adjustment



T-VEC, talimogene laherparepvec; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Our manufacturer's evidence submission presents the results of the probabilistic sensitivity analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results using the final NHS list price are presented in Table 7 below. The results including the proposed patient access scheme for talimogene laherparepvec are presented in Table 8.

Table 7 Incremental cost-effectiveness results based on PSA (NHS list price [without PAS])

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs (95% CI)
Modified Korn					
Ipilimumab	[redacted]	3.55 (3.08 to 3.94)	[redacted]	1.23 (0.58 to 1.68)	[redacted]
Talimogene laherparepvec	[redacted]	4.78 (3.97 to 5.41)			
Two-step Korn					
Ipilimumab	[redacted]	4.59 (4.20 to 4.93)	[redacted]	0.25 (-0.53 to 0.78)	[redacted]
Talimogene laherparepvec	[redacted]	4.84 (3.96 to 5.41)			

CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Table 8 Incremental cost-effectiveness results based on PSA (with PAS)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICERs (95% CI)
Modified Korn					
Ipilimumab	[redacted]	3.56 (3.12 to 3.92)	[redacted]	1.24 (0.54 to 1.73)	-£27,730 (Dominant) (-£43,936 to -£3,903)
Talimogene laherparepvec	[redacted]	4.80 (4.00 to 5.40			
Two-step Korn					
Ipilimumab	[redacted]	4.58 (4.18 to 4.95)	[redacted]	0.26 (-0.44 to 0.79)	-£1,668,400 (Dominant) (-£557,874 to £556,979)
Talimogene laherparepvec	[redacted]	4.85 (4.10 to 5.39)			

CI, confidence interval; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life-year

Figure 3 to Figure 8 present the results using scatter plots and cost-effectiveness acceptability curves.

Figure 3 Scatterplot of PSA results (1,000 simulations; results discounted, NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

[redacted]

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

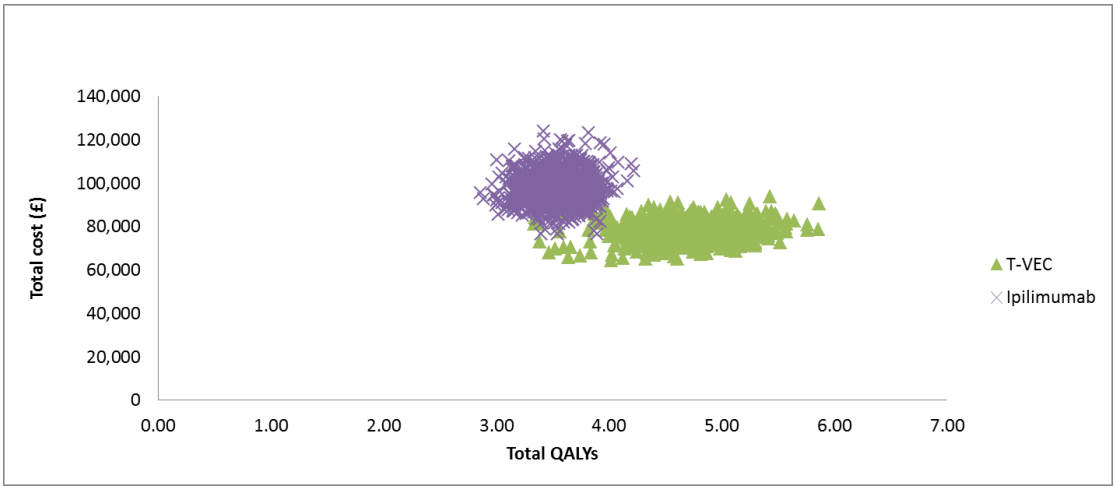
b. Using Two-Step Korn Adjustment

[redacted]

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

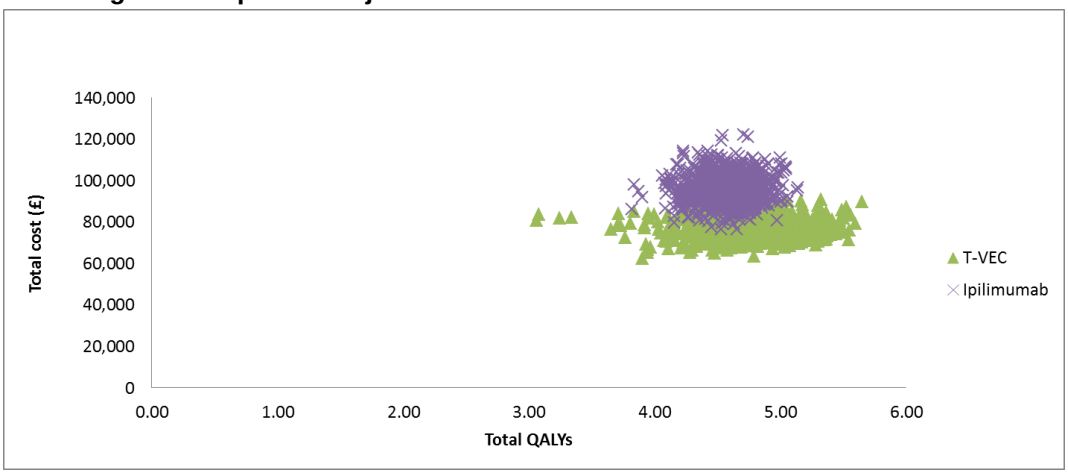
Figure 4 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

Figure 5 Scatterplot of PSA results (1,000 simulations; results discounted, NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

[redacted]

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

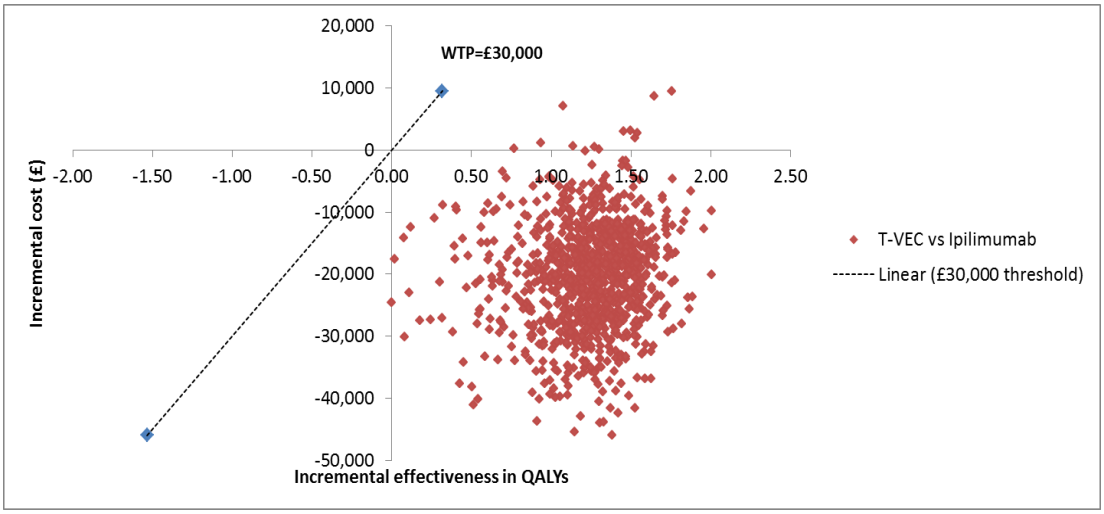
b. Using Two-Step Korn Adjustment

[redacted]

PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

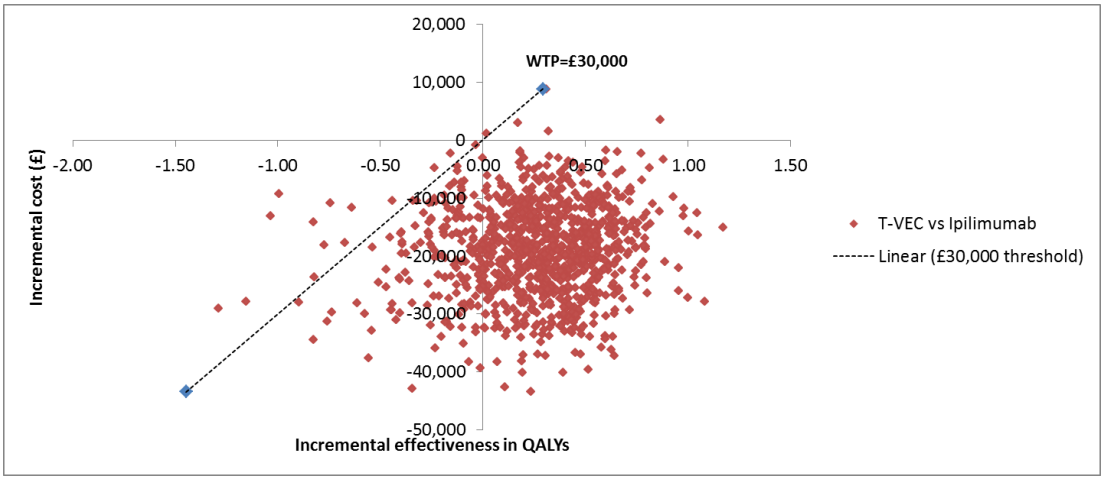
Figure 6 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

b. Using Two-Step Korn Adjustment



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec; WTP: willingness to pay.

Figure 7 Cost-effectiveness acceptability curve (results discounted, with NHS list prices for talimogene laherparepvec and ipilimumab)

a. Using Modified Korn Adjustment

[redacted]

QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

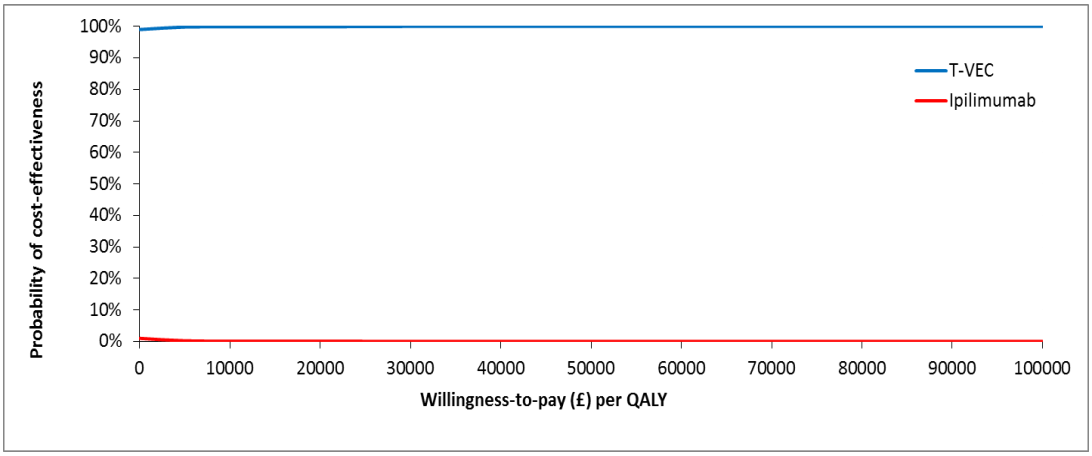
b. Using Two-Step Korn Adjustment

[redacted]

QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

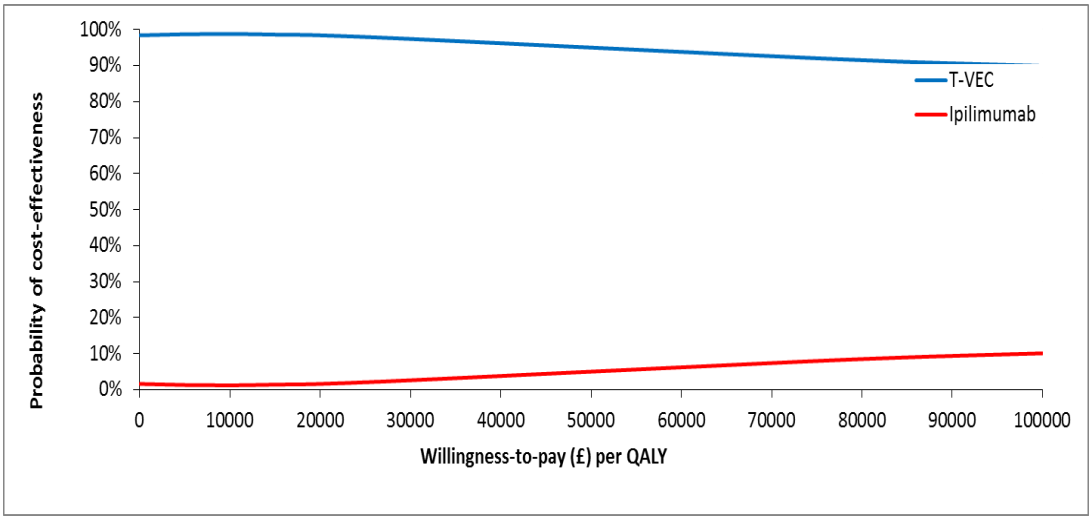
Figure 8 Cost-effectiveness acceptability curve (results discounted, with PAS price for talimogene laherparepvec and NHS list price for ipilimumab)

a. Using Modified Korn Adjustment



QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

b. Using Two-Step Korn Adjustment



QALY, quality-adjusted life-year; T-VEC: talimogene laherparepvec.

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Our manufacturer's evidence submission presents the results of the scenario analyses for talimogene laherparepvec vs. ipilimumab at the anticipated NHS list price for talimogene laherparepvec and the NHS list price for ipilimumab. The results using the final NHS list price are presented in Table 9 below.

Table 9 Results of the scenario analyses (NHS list price [without PAS])

Parameter	Base Case assumptions	Sensitivity Analysis	Modified Korn ICER	Two-Step Korn ICER
			£/QALY	£/QALY
Base case result:			[redacted]	[redacted]
Varying the time horizon				
Time horizon	30 years	10 years	[redacted]	[redacted]
		20 years	[redacted]	[redacted]
		25 years	[redacted]	[redacted]
Varying the modelling approach for T-VEC dosing				
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection[redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]

		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	[redacted]
Varying the modelling approach for IPI dosing				
IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	[redacted]	[redacted]
Varying the approach to modelling utilities				
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al., 2009 (PR = 0.85, SD = 0.77, PD = 0.59; as no value was reported for CR, it is assumed to have the same value as PR)	[redacted]	[redacted]
		IPI 1 L (TA268) (SD = 0.81, PD = 0.77; as no values were reported for CR and PR, they are assumed to have the same value as SD)	[redacted]	[redacted]
		Amgen TTO study (CR = 0.84, PR = 0.73, SD = 0.69, PD = 0.45)	[redacted]	[redacted]
Alternative parametric curve fits				
OS	Exponential	Log-normal	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]
PFS	Generalised gamma	Log-normal	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]
Alternative approach to modelling survival				
OS	3-part curve fit	2-part curve fit	[redacted]	[redacted]
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	[redacted]

Varying resource use assumptions in terminal care				
Cost of terminal care	Amgen resource use study	TA319 (£6,211.006 [inflated from 2012 cost to 2015 cost])	[redacted]	[redacted]
Varying resource use assumptions in routine treatment for non-progressive disease				
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR were £0.00 for both T-VEC and IPI	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	[redacted]
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	[redacted]
BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; QALY, quality-adjusted life-year; SD, stable disease; SPC, summary of product characteristics; TTO, time trade off; T-VEC, talimogene laherparepvec				

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

The cost-effectiveness results of scenario analyses including the proposed patient access scheme for talimogene laherparepvec are presented in Table 10 below.

Table 10 Results showing the impact of patient access scheme on ICERs

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
Base case result:			[redacted]	-£16,367	[redacted]	-£60,271
Varying the time horizon						
Time horizon	30 years	10 years	[redacted]	-£28,575	[redacted]	-£116,708
		20 years	[redacted]	-£18,867	[redacted]	-£71,402
		25 years	[redacted]	-£17,193	[redacted]	-£63,624
Varying the modelling approach for T-VEC dosing						
T-VEC dosing	Excludes accelerated dosing and includes extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	Includes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	-£14,704	[redacted]	-£53,840

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
		Excludes accelerated dosing and extension phase First dose: [redacted] Subsequent doses: [redacted] Mean number of injections post first injection: [redacted] Total number of vials: [redacted]	[redacted]	-£19,389	[redacted]	-£71,957
Varying the modelling approach for IPI dosing						
IPI dosing	Dose: 5.22 vials (261 mg/3 weeks) Treatment duration: 3.5 doses over 10.5 weeks Source/assumption: BMS second-line IPI NICE submission, 2012	Dose: 5 vials (250 mg/3 weeks) Treatment duration: 4 doses over 12 weeks Source/assumption: SPC assuming weight range =(70kg - 81.8kg)	[redacted]	-£21,253	[redacted]	-£79,163

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
Varying the approach to modelling utilities						
Source of utility estimates	Dabrafenib NICE submission	Beusterien et al., 2009 (PR = 0.85, SD = 0.77, PD = 0.59; as no value was reported for CR, it is assumed to have the same value as PR)	[redacted]	-£16,163	[redacted]	-£69,918
		IPI 1 L (TA268) (SD = 0.81, PD = 0.77; as no values were reported for CR and PR, they are assumed to have the same value as SD)	[redacted]	-£15,431	[redacted]	-£53,870
		Amgen TTO study (CR = 0.84, PR = 0.73, SD = 0.69, PD = 0.45)	[redacted]	-£17,701	[redacted]	-£71,742
Alternative parametric curve fits						
OS	Exponential	Log-normal	[redacted]	-£14,644	[redacted]	-£48,610
		Weibull	[redacted]	-£14,601	[redacted]	-£47,977
PFS	Generalised gamma	Log-normal	[redacted]	-£18,338	[redacted]	-£88,189

Parameter	Base Case assumptions	Sensitivity Analysis	ICER for talimogene laherparepvec versus ipilimumab			
			Modified Korn ICER		Two-Step Korn ICER	
			£/QALY		£/QALY	
			Without PAS (NHS list price)	With PAS	Without PAS (NHS list price)	With PAS
		Log-logistic	[redacted]	-£18,380	[redacted]	-£87,422
Alternative approach to modelling survival						
OS	3-part curve fit	2-part curve fit	[redacted]	-£14,108	[redacted]	-£27,241
PFS	Adjust long-term T-VEC PFS	Do not adjust long-term T-VEC PFS	[redacted]	-£16,739	[redacted]	-£59,667
Varying resource use assumptions in terminal care						
Cost of terminal care	Amgen resource use study	TA319 (£6,211.006 [inflated from 2012 cost to 2015 cost])	[redacted]	-£16,372	[redacted]	-£60,277
Varying resource use assumptions in routine treatment for non-progressive disease						
Costs of routine treatment for non-progressive disease	Costs of routine treatment with CR are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR were £0.00 for both T-VEC and IPI	[redacted]	-£17,769	[redacted]	-£65,967
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD reduced by 20% (£69.22)	[redacted]	-£17,310	[redacted]	-£63,722
	Costs of routine treatment with CR, PR, SD, and PD are £86.52 for both T-VEC and IPI	Costs of routine treatment with CR, PR, SD, and PD increased by 20% (£103.83)	[redacted]	-£15,424	[redacted]	-£56,820

BMS, Bristol Myers Squibb; CR, complete response; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; OS, overall survival; PAS, patient access scheme; PD, progressive disease; PFS, progression-free survival; PR, partial response; QALY, quality-adjusted life-year; SD, stable disease; SPC, summary of product characteristics; TTO, time trade off; T-VEC, talimogene laherparepvec

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.