NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [ID811]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Bristol-Myers Squibb Pharmaceuticals**
   - **Roy Castle Lung Cancer Foundation**
   - **British Thoracic Society**

   Royal College of Physicians endorses the British Thoracic Society response

   'No comment' response received from the Department of Health and from Matthew Hatton and Sanjay Popat (clinical experts)

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Company new evidence** prepared by Bristol-Myers Squibb Pharmaceuticals

5. **Evidence Review Group critique of company new evidence**

6. **Company PAS submission** – prepared by Bristol-Myers Squibb Pharmaceuticals

   Evidence Review Group – critique of company PAS submission - to follow

   Evidence Review Group addendum – to follow

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Bristol-Myers Squibb	**Summary remarks** Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd disagree with the proposed recommendation for nivolumab for previously treated locally advanced or metastatic squamous NSCLC.	Thank you for your comments.
	BMS would request the committee re-consider the extrapolation of overall survival (OS) to inform the CE modelling (Section 4.8 of the ACD). The original model submitted to NICE was based on a minimum follow-up of 12 months from the CheckMate 017 study. Since the submission of the original model, 18-months follow-up data has become available (this was provided at the clarification question phase). The original approach to predict OS beyond the trial period was therefore re-run using the 18-month dataset – that is identifying the best fitting extrapolation. These results show that both the 18-month and 12-month data fits best with the OS log-logistic extrapolation model.	The committee considered in detail the extrapolation of overall survival in the company's and the ERG's analyses. Please see sections 4.9–4.11 in the Final Appraisal Determination (FAD).
	Furthermore, the OS KM curves from the study do not show a need to adopt a piecewise extrapolation approach of using KM data up to 40 weeks followed by an exponential function as recommended by the ERG – that is, no single assessment is driving the distribution of the curve. Therefore, it would be more robust to use the entire dataset and identify a parametric distribution for the full time horizon of the model, as recommended by the NICE DSU guidance (see Appendix 1).	
	Section 4.9 of the ACD discusses the quality of life data presented in BMS original submission. The committee conclude that it is ''reasonable to consider that the most appropriate values would be between those presented by the company and those from the ERG''. BMS assert the values collected in CheckMate 017 are the most appropriate and robust for this appraisal and note these values are in line with the NICE reference case. We provide further justification for the use of these values in Appendix 1.	The committee considered the alternative health state utility values presented in the company's revised analyses. It concluded that it would be reasonable to use utility values of 0.693 (progression-free state) and 0.509 (progressed-disease state) for decision-making. Please see section 4.13 of the FAD.
	BMS have provided a revised base-case ICER taking into account the points above. These results in an ICER for nivolumab vs. docetaxel of £91,870 / QALY. In its	The committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for

Consultee	Comment [sic]	Response
	further deliberations, BMS would ask the committee to further consider the importance of duration of therapy for nivolumab. **<u>Duration of Therapy</u>** There is uncertainty as to the optimal duration of therapy for nivolumab and it may be feasible to stop nivolumab treatment before a patient progresses and for that patient to maintain clinical benefit. This is based on the mechanism of action of nivolumab, which upregulates the activity of T cells that in turn act against the tumour, and this activity remains after the administration of the drug is withdrawn. It is notable that in CheckMate 017, only 19% of patients remained on treatment with nivolumab at one year, and only a small number of patients remained on treatment for a significantly longer period of time. Uncertainty remains about how long this group of patients should be treated for. Data examining the relative clinical efficacy of stopping nivolumab in patients after one year of therapy will become available during the course of this appraisal and details of this study (CheckMate 153) are contained within the dossier. In order to reflect the uncertainty in optimal duration of treatment, BMS included two sensitivity analyses in the submission examining the cost effectiveness of stopping treatment after 1 and 2 years (referred to as the 1 and 2 year 'stopping rules'). The choice of these stopping rules was rational and based on existing and anticipated data, and the underlying mechanism of action of nivolumab and clinical opinion. Evidence to support this approach is provided in study CheckMate 003, in which patients were treated up to 96 weeks and then stopped treatment (Gettinger 2015). As can be seen from Figure 31 in the original submission), 7 of 22 responders stopped nivolumab at the pre-defined stopping point of 96 weeks. In each of these responders, there was a significant ongoing response beyond 96 weeks (indeed, at the last analysis, six of the seven responders had still not progressed), demonstrating an ongoing clinical benefit despite withdrawal of nivolumab, and supporting the hypothesis that stopping nivolumab treatment at a pre-defined time point whilst maintaining clinical benefit may be feasible. Sensitivity analyses of treatment-stopping rules at 1 year and 2 years which limit duration of treatment accordingly, result in ICERs of £61,555 and £80,306, versus docetaxel. This suggests that, as duration of treatment is reduced, the ICER is reduced and is more in line with an anticipated real world setting. BMS is committed to addressing the question of optimal duration of treatment of nivolumab in lung cancer. A Phase III study, CheckMate 153, is ongoing and in this	nivolumab compared with docetaxel was at least £140,000 per quality-adjusted life year (QALY) gained. Please see section 4.22 of the FAD. Thank you for your comments on optimal duration of treatment with nivolumab. The committee considered that it would be appropriate to consider this guidance for review when results from the CheckMate-153 trial become available. Please see section 4.17 of the FAD.

Consultee	Comment [sic]	Response
	study, responders to nivolumab are randomised at 1 year to either discontinue or to continue nivolumab treatment until progression. Availability of data from CheckMate 153 is anticipated [redacted]. Furthermore, within the recent FAD for nivolumab for the treatment of melanoma, the Institute noted there is uncertainty around the likely duration of treatment and therefore recommended a review of the guidance in two years, at which point overall survival data will be considerably more mature, and it might be possible to clarify optimum treatment duration. **Conclusion** Nivolumab is the first new drug for patients with previously treated, locally advanced or metastatic squamous NSCLC to become available in over 10 years. It is also the first PD-1 inhibitor to demonstrate a clinically significant survival benefit in locally advanced or metastatic squamous NSCLC. Nivolumab was designated as a Promising Innovative Medicine (PIM) by the Medicines and Healthcare products Regulatory Authority and is also approved through the Early Access to Medicines Scheme (EAMS) both for pre-treated squamous NSCLC, previously untreated and pre-treated melanoma patients. Nivolumab provides an unprecedented survival benefit (41% reduction in mortality compared with standard of care) in patients where no new treatments have been made available, representing a step-change in the management of advanced squamous NSCLC. Therefore, we believe it is in the interest of patients that BMS continue to work with NICE and NHS to find ways to ensure nivolumab can be made available for routine use in the NHS.	The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. However it noted that no evidence had been presented to suggest that there were benefits that had not already been captured within the economic modelling. Please see sections 4.19 and 4.22 of the FAD.

Consultee	Comment [sic]	Response
British Thoracic Society	**ACD - Consultees & Commentators: Lung cancer (non-small-cell, squamous, metastatic) - nivolumab (after chemotherapy) [811]** Thank you for inviting comments from the British Thoracic Society on this appraisal consultation document. Nivolumab is very effective second line treatment for NSCLC but we note it is above the NICE cost effectiveness cut off and so this will not be recommended. This is very disappointing - the British Thoracic Society believes Nivolumab to be an extremely novel and effective treatment for advanced lung cancer in a group of patients for which there is very little other treatment available, and we urge NICE to enter into negotiations with the company to reach a compromise on the cost effectiveness.	Thank you for your comments. The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. It understood that nivolumab is innovative, both in its therapeutic approach and its clinical effectiveness, and that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy. However, the most plausible ICER for nivolumab compared with docetaxel would be at least £140,000 per QALY gained. Therefore, the committee did not recommend nivolumab as a cost-effective use of NHS resources. Please see sections 4.2, 4.19 and 4.22 of the FAD.

Consultee	Comment [sic]	Response
Roy Castle Lung Cancer Foundation	**Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Nivolumab for previously treated, locally advanced or metastatic squamous non small cell lung cancer.** **This response is submitted by Roy Castle Lung Cancer Foundation.** • We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Nivolumab in this indication. • We welcome many of the conclusions reached by the Appraisal Committee in this ACD o Nivolumab is a clinically effective treatment option for previously treated squamous non small cell lung cancer (section 4.3) o Nivolumab is an innovative therapy, both in its therapeutic approach and in its clinical effectiveness (section 4.14) o Nivolumab meets the criteria of a life extending, end of life treatment (section 4.16) • We note that the Appraisal Committee has reached this negative decision, based solely on cost issues - Nivolumab, having not been deemed a cost effective use of NHS resources. (section 4.17). We note the Manufacturer's base case ICER was £86,000 per QALY gained, with the Appraisal Committee concluding that the "most plausible incremental cost-effectiveness ration for Nivolumab, compared with Docetaxel is between £109,000 and £129,000 per quality adjusted life year gained". • **On behalf of the many lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues are addressed**. Advanced Lung cancer remains a devastating disease for many. We hope that compromise and agreement on price can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	Thank you for your comments. The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. It understood that nivolumab is innovative, both in its therapeutic approach and its clinical effectiveness, and that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy. However, the most plausible ICER for nivolumab compared with docetaxel would be at least £140,000 per QALY gained. Therefore, the committee did not recommend nivolumab as a cost-effective use of NHS resources. Please see sections 4.2, 4.19 and 4.22 of the FAD.

The Royal College of Physicians stated that it endorsed the comments from the British Thoracic Society.
The Department of Health stated that it had no comments on the appraisal consultation document.

Comments received from clinical experts and patient experts

Matthew Hatton and Sanjay Popat stated that they had no comments on the Appraisal Consultation Document.

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Health professional (within NHS)		Lung cancer is the biggest cause of early death in the UK, higher than all cardiac disease combined. THere has been many new treatments for lung adenocarcinoma which has been approved and has extended lung cancer patients' lives, but not for squamous carcinoma. This is the first advance in more than a decade that actually made a difference in squamous cell carcinoma patients; some of whom will be long term responders. It is such a pity that a negotiation with drug company cannot be initiatied to allow for this treatment to be availabel for lung cancer paitnets	Thank you for your comments. The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. It understood that nivolumab is innovative, both in its therapeutic approach and its clinical effectiveness, and that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy. However, the most plausible ICER for nivolumab compared with docetaxel would be at least £140,000 per QALY gained. Therefore, the committee did not recommend nivolumab as a cost-effective use of NHS resources. Please see sections 4.2, 4.19 and 4.22 of the FAD.

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

Role*	Section	Comment [sic]	Response
Health professional (private sector)		Extremely disappointing decision not to fund treatment which would represent a great step forward for a small group of patients with NSCLC for whom a 3 month improvement in median survival is a huge step forward. Not to be utilising immunotherapy for lung cancer patients puts us out of step with our first world oncology colleagues.	Thank you for your comments. The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. It understood that nivolumab is innovative, both in its therapeutic approach and its clinical effectiveness, and that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy. However, the most plausible ICER for nivolumab compared with docetaxel would be at least £140,000 per QALY gained. Therefore, the committee did not recommend nivolumab as a cost-effective use of NHS resources. Please see sections 4.2, 4.19 and 4.22 of the FAD.
Other – patient advocate		Professor Andrew Stevens Chair of Appraisal Committee C, Professor of Public Health University of Birmingham National Institute for Health and Care Excellence (NICE) Re: Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer Dear Professor Stevens and Appraisal Committee C Colleagues, We are writing to encourage the Appraisal Committee to reconsider its December, 2015 decision, based on the Evidence Review Group (ERG) report from the Liverpool Reviews and Implementation Group which led to NICE's adverse decision as to the use of nivolumab for the indication of locally advanced or metastatic squamous NSCLC in the NHS in England. ICAN, International Cancer Advocacy Network, http://www.askican.org, is a Phoenix, Arizona-based charitable organization (EIN 86-0818253), founded in 1996, with the mission of providing cutting-edge information services and empowerment tools to Stage IV cancer patients in all 50 states and in 53 countries, including the United Kingdom. For the very small patient population in the UK which has been diagnosed	Thank you for your comments. The committee was aware that nivolumab is a clinically-effective treatment option, and that it is considered a very important development in treating squamous NSCLC. It understood that nivolumab is innovative, both in its therapeutic approach and its clinical effectiveness, and that there is an important unmet need for people with squamous NSCLC whose disease has progressed after chemotherapy. However, the most plausible ICER for nivolumab compared with docetaxel would be at least £140,000 per QALY gained. Therefore, the committee did not recommend nivolumab as a cost-effective use of NHS resources. The company's economic model incorporated costs including managing adverse events, patient monitoring, disease management and care at the

Role*	Section	Comment [sic]	Response
		with metastatic squamous NSCLC, nivolumab should be considered an important treatment option for the UK medical oncologist/thoracic oncologist. Patients should have covered access to nivolumab within the NHS to prolong their lives with a higher quality of life given nivolumab's eminently manageable toxicity profile. For metastatic squamous non small cell lung cancer patients, life expectancy is short, as there is a lack of therapeutic options in second-line treatment. We urge NICE to consider the cost savings to the NHS if nivolumab were approved as a second-line treatment versus the higher costs to NHS of the Accident and Emergency (A & E) admissions attributable to the toxicities of second line systemic therapy or best supportive care. We write not as bioinformaticists, statisticians, health economists, or clinicians. We are patient advocates using a Tumour Board approach to cancer cases, involving members of our Physicians Advisory Council, our Biomarkers Council, and our Scientific Advisory Council. Our NSCLC patients in the United States are overseen by leading thoracic oncologists in both comprehensive cancer centers and the community oncology setting. Since we deal exclusively with Stage IV patients, our patient population tends to be heavily pre-treated, and we routinely initiate discussions regarding clinical trials and expanded access with each patient during the course of his or her journey with cancer. We empower shared decision-making between metastatic NSCLC patients and their medical teams. It is important to note that since the initial submission by Bristol Myers-Squibb in 2015, there has been rapid uptake in the United States of nivolumab. Virtually every major medical center in the Phoenix and Scottsdale-Arizona area is using this promising immunotherapy from two centers that are affiliated with comprehensive cancer centers to major medical centers and community oncology practices which handle many cancer patients. Indeed, there is no question that nivolumab is the new standard of care throughout the United States within its indications for melanoma, NSCLC, and RCC. At the 10th Annual New York Lung Cancer Symposium, hosted by the Physicians Education Resource, on November 7, 2015, Renato G. Martins, MD, MPH, Seattle Cancer Care Alliance's medical director for thoracic/head and neck oncology, told onclive.com interviewer and writer	end of life. Please see sections 3.8, 4.2, 4.19 and 4.22 of the FAD.

Role*	Section	Comment [sic]	Response
		Anita T. Shaffer (PD-1 Inhibitors Advance Rapidly for Broad Cohort in NSCLC) that as of now, I don't think that any patient is clearly not a candidate for these (checkpoint inhibitors). Every patient with non-small cell lung cancer would potentially be a candidate in the second-line setting. Moreover, Roman Perez-Soler, MD, deputy director of the Albert Einstein Cancer Center in Bronx, New York, and chairman of the Department of Oncology at Montefiore Medical Center, stated: The dream here and what would make a big difference is the possibility that a small group of patients with stage IV non-small cell lung cancer can actually be cured. Dr. Perez-Soler further stated that PD-1 inhibitors are the first choice for second-line therapy in the context of squamous NSCLC. (Shaffer, www.onclive.com) Because of nivolumabs impressive clinical trials data and the anecdotal reports of the leading thoracic oncologists who have helped draft the National Comprehensive Cancer Network (NCCN) NSCLC Guidelines, the NCCN classified nivolumab as "category 1" in its most recent update and thus views nivolumab as a preferred second-line therapy for patients who have progressive disease following a chemotherapy doublet. While ICANs patient data are maintained by their home treatment centers and while ICAN does not have final data beyond clinical trials and anecdotal reports, our patient advocates continue to observe impressive responses in NSCLC/squamous patients. We are excited about this drug in additional solid tumors such as renal cell carcinoma and in the context of clinical trials for other solid tumors and blood cancers. The experience of one of our renal cell carcinoma patients whose performance status was most precarious at the start of nivolumab treatment is a testament to this exciting immuno-oncology product. This particular patient was literally brought "back from the precipice" and is now enjoying far more functionality and overall quality of life. Before administration of nivolumab, this patient's prognosis was dire, and he was close to being written off. The patient had been heavily pre-treated with systemic therapies and targeted therapies thus, in far worse condition than any of our lung cancer patients on the verge of receiving second-line therapy. What ICAN patient advocates have learned from this RCC patient anecdote is that nivolumab has the potential to save both the US health care system as well as the NHS tremendous costs associated not only vis a vis hospital admissions attributable to the toxicities of systemic therapies	

Role*	Section	Comment [sic]	Response
		but with home health care visits for metastatic squamous NSCLC patients as well. ICAN endorses the opinions of the consultees and commentators in support of nivolumab and the testimony from the original hearing before the Appraisal Committee. On behalf of metastatic squamous UK lung cancer patients with limited therapeutic options and a shortened life expectancy, we respectfully urge your reconsideration of the Appraisal Consultation Document. Thank you. [redacted]	

BMS response to the Appraisal Consultation Document (ACD) for nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC)

Summary remarks

Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd disagree with the proposed recommendation for nivolumab for previously treated locally advanced or metastatic squamous NSCLC.

BMS would request the committee re-consider the extrapolation of overall survival (OS) to inform the CE modelling (Section 4.8 of the ACD). The original model submitted to NICE was based on a minimum follow-up of 12 months from the CheckMate 017 study. Since the submission of the original model, 18-months follow-up data has become available (this was provided at the clarification question phase). The original approach to predict OS beyond the trial period was therefore re-run using the 18-month dataset – that is identifying the best fitting extrapolation. These results show that both the 18-month and 12-month data fits best with the OS log-logistic extrapolation model.

Furthermore, the OS KM curves from the study do not show a need to adopt a piecewise extrapolation approach of using KM data up to 40 weeks followed by an exponential function as recommended by the ERG – that is, no single assessment is driving the distribution of the curve. Therefore, it would be more robust to use the entire dataset and identify a parametric distribution for the full time horizon of the model, as recommended by the NICE DSU guidance (see Appendix 1).

Section 4.9 of the ACD discusses the quality of life data presented in BMS original submission. The committee conclude that it is ''reasonable to consider that the most appropriate values would be between those presented by the company and those from the ERG''. BMS assert the values collected in CheckMate 017 are the most appropriate and robust for this appraisal and note these values are in line with the NICE reference case. We provide further justification for the use of these values in Appendix 1.

BMS have provided a revised base-case ICER taking into account the points above. These results in an ICER for nivolumab vs. docetaxel of £91,870 / QALY. In its further deliberations, BMS would ask the committee to further consider the importance of duration of therapy for nivolumab.

Duration of Therapy

There is uncertainty as to the optimal duration of therapy for nivolumab and it may be feasible to stop nivolumab treatment before a patient progresses and for that patient to maintain clinical benefit. This is based on the mechanism of action of nivolumab, which upregulates the activity of T cells that in turn act against the tumour, and this activity remains after the administration of the drug is withdrawn.

It is notable that in CheckMate 017, only 19% of patients remained on treatment with nivolumab at one year, and only a small number of patients remained on treatment for a significantly longer period of time. Uncertainty remains about how long this group of patients should be treated for. Data examining the relative clinical efficacy of stopping nivolumab in patients after one year of therapy will become available during the course of this appraisal and details of this study (CheckMate 153) are contained within the dossier.

In order to reflect the uncertainty in optimal duration of treatment, BMS included two sensitivity analyses in the submission examining the cost effectiveness of stopping treatment after 1 and 2 years (referred to as the 1 and 2 year 'stopping rules'). The choice of these stopping rules was rational and based on existing and anticipated data, and the underlying mechanism of action of nivolumab and clinical opinion.

Evidence to support this approach is provided in study CheckMate 003, in which patients were treated up to 96 weeks and then stopped treatment (Gettinger 2015). As can be seen from **Error! Reference source not found.** in the original submission), 7 of 22 responders stopped nivolumab at the pre-defined stopping point of

96 weeks. In each of these responders, there was a significant ongoing response beyond 96 weeks (indeed, at the last analysis, six of the seven responders had still not progressed), demonstrating an ongoing clinical benefit despite withdrawal of nivolumab, and supporting the hypothesis that stopping nivolumab treatment at a pre-defined time point whilst maintaining clinical benefit may be feasible.

Sensitivity analyses of treatment-stopping rules at 1 year and 2 years which limit duration of treatment accordingly, result in ICERs of £61,555 and £80,306, versus docetaxel. This suggests that, as duration of treatment is reduced, the ICER is reduced and is more in line with an anticipated real world setting.

BMS is committed to addressing the question of optimal duration of treatment of nivolumab in lung cancer. A Phase III study, CheckMate 153, is ongoing and in this study, responders to nivolumab are randomised at 1 year to either discontinue or to continue nivolumab treatment until progression. Availability of data from CheckMate 153 is anticipated [redacted].

Furthermore, within the recent FAD for nivolumab for the treatment of melanoma, the Institute noted there is uncertainty around the likely duration of treatment and therefore recommended a review of the guidance in two years, at which point overall survival data will be considerably more mature, and it might be possible to clarify optimum treatment duration.

Conclusion

Nivolumab is the first new drug for patients with previously treated, locally advanced or metastatic squamous NSCLC to become available in over 10 years. It is also the first PD-1 inhibitor to demonstrate a clinically significant survival benefit in locally advanced or metastatic squamous NSCLC. Nivolumab was designated as a Promising Innovative Medicine (PIM) by the Medicines and Healthcare products Regulatory Authority and is also approved through the Early Access to Medicines Scheme (EAMS) both for pre-treated squamous NSCLC, previously untreated and pre-treated melanoma patients. Nivolumab provides an unprecedented survival benefit (41% reduction in mortality compared with standard of care) in patients where no new treatments have been made available, representing a step-change in the management of advanced squamous NSCLC. Therefore, we believe it is in the interest of patients that BMS continue to work with NICE and NHS to find ways to ensure nivolumab can be made available for routine use in the NHS.

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Nivolumab for previously treated, locally advanced or metastatic squamous non small cell lung cancer.

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Nivolumab in this indication.

- We welcome many of the conclusions reached by the Appraisal Committee in this ACD

    - Nivolumab is a clinically effective treatment option for previously treated squamous non small cell lung cancer (section 4.3)

    - Nivolumab is an innovative therapy, both in its therapeutic approach and in its clinical effectiveness (section 4.14)

    - Nivolumab meets the criteria of a life extending, end of life treatment (section 4.16)

- We note that the Appraisal Committee has reached this negative decision, based solely on cost issues - Nivolumab, having not been deemed a cost effective use of NHS resources. (section 4.17).
  We note the Manufacturer's base case ICER was £86,000 per QALY gained, with the Appraisal Committee concluding that the "most plausible incremental cost-effectiveness ration for Nivolumab, compared with Docetaxel is between £109,000 and £129,000 per quality adjusted life year gained".

- **On behalf of the many lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues are addressed**. Advanced Lung cancer remains a devastating disease for many. We hope that compromise and agreement on price can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.

Roy Castle Lung Cancer Foundation
January 2016

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Company Registration No. 1645201

NICE
Via NICE docs

18 January 2016

Dear Colleague,

ACD - Consultees & Commentators: Lung cancer (non-small-cell, squamous, metastatic) - nivolumab (after chemotherapy) [811]

Thank you for inviting comments from the British Thoracic Society on this appraisal consultation document.

Nivolumab is very effective second line treatment for NSCLC but we note it is above the NICE cost effectiveness cut off and so this will not be recommended.

This is very disappointing - the British Thoracic Society believes Nivolumab to be an extremely novel and effective treatment for advanced lung cancer in a group of patients for which there is very little other treatment available, and we urge NICE to enter into negotiations with the company to reach a compromise on the cost effectiveness.

Yours sincerely

[redacted]

[redacted]

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	Consultant Clinical Oncologist
Location	England
Conflict	No
Disclosure	
Comments	Lung cancer is the biggest cause of early death in the UK, higher than all cardiac disease combined. THere has been many new treatments for lung adenocarcinoma which has been approved and has extended lung cancer patients' lives, but not for squamous carcinoma. This is the first advance in more than a decade that actually made a difference in squamous cell carcinoma patients; some of whom will be long term responders. It is such a pity that a negotiation with drug company cannot be initiatied to allow for this treatment to be availabel for lung cancer paitnets
Submission date	

Name	[redacted]
Organisation	
Role	Private Sector Professional
Job title	Consultant Clinical Oncologist
Location	England
Conflict	Yes
Disclosure	I have participated in Clinical trials run by BMS in the past
Comments	Extremely disappointing decision not to fund treatment which would represent a great step forward for a small group of patients with NSCLC for whom a 3 month improvement in median survival is a huge step forward. Not to be utilising immunotherapy for lung cancer patients puts us out of step with our first world oncology colleagues.
Submission date	

Name	[redacted]
Organisation	International Cancer Advocacy Network (ICAN)
Role	Patient Advocate
Job title	[redacted]
Location	United States
Conflict	No
Disclosure	
Comments	Professor Andrew Stevens Chair of Appraisal Committee C, Professor of Public Health University of Birmingham National Institute for Health and Care Excellence (NICE) Re: Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer Dear Professor Stevens and Appraisal Committee C

	Colleagues, We are writing to encourage the Appraisal Committee to reconsider its December, 2015 decision, based on the Evidence Review Group (ERG) report from the Liverpool Reviews and Implementation Group which led to NICE's adverse decision as to the use of nivolumab for the indication of locally advanced or metastatic squamous NSCLC in the NHS in England. ICAN, International Cancer Advocacy Network, http://www.askican.org, is a Phoenix, Arizona-based charitable organization (EIN 86-0818253), founded in 1996, with the mission of providing cutting-edge information services and empowerment tools to Stage IV cancer patients in all 50 states and in 53 countries, including the United Kingdom. For the very small patient population in the UK which has been diagnosed with metastatic squamous NSCLC, nivolumab should be considered an important treatment option for the UK medical oncologist/thoracic oncologist. Patients should have covered access to nivolumab within the NHS to prolong their lives with a higher quality of life given nivolumab's eminently manageable toxicity profile. For metastatic squamous non small cell lung cancer patients, life expectancy is short, as there is a lack of therapeutic options in second-line treatment. We urge NICE to consider the cost savings to the NHS if nivolumab were approved as a second-line treatment versus the higher costs to NHS of the Accident and Emergency (A & E) admissions attributable to the toxicities of second line systemic therapy or best supportive care. We write not as bioinformaticists, statisticians, health economists, or clinicians. We are patient advocates using a Tumour Board approach to cancer cases, involving members of our Physicians Advisory Council, our Biomarkers Council, and our Scientific Advisory Council. Our NSCLC patients in the United States are overseen by leading thoracic oncologists in both comprehensive cancer centers and the community oncology setting. Since we deal exclusively with Stage IV patients, our patient population tends to be heavily pre-treated, and we routinely initiate discussions regarding clinical trials and expanded access with each patient during the course of his or her journey with cancer. We empower shared decision-making between metastatic NSCLC patients and their medical teams. It is important to note that since the initial submission by Bristol Myers-Squibb in 2015, there has been rapid uptake in the United States of nivolumab. Virtually every major medical center in the Phoenix and Scottsdale-Arizona area is using this promising immunotherapy from two centers that are affiliated with comprehensive cancer centers to major medical centers and community oncology practices which handle many cancer

	patients. Indeed, there is no question that nivolumab is the new standard of care throughout the United States within its indications for melanoma, NSCLC, and RCC. At the 10th Annual New York Lung Cancer Symposium, hosted by the Physicians Education Resource, on November 7, 2015, Renato G. Martins, MD, MPH, Seattle Cancer Care Alliance's medical director for thoracic/head and neck oncology, told onclive.com interviewer and writer Anita T. Shaffer (PD-1 Inhibitors Advance Rapidly for Broad Cohort in NSCLC) that as of now, I don't think that any patient is clearly not a candidate for these (checkpoint inhibitors). Every patient with non-small cell lung cancer would potentially be a candidate in the second-line setting. Moreover, Roman Perez-Soler, MD, deputy director of the Albert Einstein Cancer Center in Bronx, New York, and chairman of the Department of Oncology at Montefiore Medical Center, stated: The dream here and what would make a big difference is the possibility that a small group of patients with stage IV non-small cell lung cancer can actually be cured. Dr. Perez-Soler further stated that PD-1 inhibitors are the first choice for second-line therapy in the context of squamous NSCLC. (Shaffer, www.onclive.com) Because of nivolumabs impressive clinical trials data and the anecdotal reports of the leading thoracic oncologists who have helped draft the National Comprehensive Cancer Network (NCCN) NSCLC Guidelines, the NCCN classified nivolumab as "category 1" in its most recent update and thus views nivolumab as a preferred second-line therapy for patients who have progressive disease following a chemotherapy doublet. While ICANs patient data are maintained by their home treatment centers and while ICAN does not have final data beyond clinical trials and anecdotal reports, our patient advocates continue to observe impressive responses in NSCLC/squamous patients. We are excited about this drug in additional solid tumors such as renal cell carcinoma and in the context of clinical trials for other solid tumors and blood cancers. The experience of one of our renal cell carcinoma patients whose performance status was most precarious at the start of nivolumab treatment is a testament to this exciting immuno-oncology product. This particular patient was literally brought "back from the precipice" and is now enjoying far more functionality and overall quality of life. Before administration of nivolumab, this patient's prognosis was dire, and he was close to being written off. The patient had been heavily pre-treated with systemic therapies and targeted therapies thus, in far worse condition than any of our lung cancer patients on the verge of receiving second-line therapy. What ICAN patient

	advocates have learned from this RCC patient anecdote is that nivolumab has the potential to save both the US health care system as well as the NHS tremendous costs associated not only vis a vis hospital admissions attributable to the toxicities of systemic therapies but with home health care visits for metastatic squamous NSCLC patients as well. ICAN endorses the opinions of the consultees and commentators in support of nivolumab and the testimony from the original hearing before the Appraisal Committee. On behalf of metastatic squamous UK lung cancer patients with limited therapeutic options and a shortened life expectancy, we respectfully urge your reconsideration of the Appraisal Consultation Document. Thank you. [redacted] (ICAN) [redacted];
Submission date	

ACD appendix 1: ACD for nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC)

This appendix provides additional analyses to support the appraisal committee in its deliberations and reflects comments made by the committee in the ACD and also, comments made by the ERG in the ERG assessment report. We are happy to provide additional analyses should these be helpful to the committee.

Overall and progression-free survival ACD response

Overall survival:

Upon review of the ACD document it is acknowledged that the Committee had three main concerns regarding overall survival (Section 4.8 of the ACD document):

1. Projection of overall survival (OS) beyond the trial period,
2. Mortality rates predicted by the survival models; and
3. Benefit of nivolumab beyond progression

The original model submitted to the Instutute was based on a minimum follow-up of 12 months from the CheckMate 017 study. Since the submission of the original model, 18-month follow-up data have become available. The original approach to predict OS beyond the trial period was therefore re-run using the 18-month dataset – that is, identifying the best fitting parametric model in terms of both AIC/BIC criteria and clinical plausibility. The analysis of the 18-month data reconfirmed that the two best fitting parametric models were consistent with the original model using the 12-month data –the log-logistic and 2-spline hazards model were the best fitting parametric distributions (Table 1).

Table 1: Best fitting parametric models for OS using 18-month CheckMate 017 dataset

Distribution	AIC	BIC
Log-logistic	**1554.948974**	**1565.766**
Spline 2 knot(s) - hazard	**1555.854696**	**1573.884**
Spline 1 knot(s) - odds	1556.899209	1571.322
Spline 1 knot(s) - hazard	1557.333655	1571.757
Spline 2 knot(s) - normal	1557.418331	1575.447
Log-normal	1557.924376	1568.742
Spline 2 knot(s) - odds	1558.013751	1576.043
Generalized gamma	1558.269969	1572.693
Spline 1 knot(s) - normal	1558.608235	1573.031
Gamma	1568.110472	1578.928
Exponential	1568.992345	1576.204
Weibull	1569.994331	1580.812
Gompertz	1569.995768	1580.813

In light of the additional availability of the follow-up data, the base-case model has been updated to reflect the parameters associated with the log-logistic and 2-spline hazards distributions using the 18-month dataset.

In addition, the committee discussed that the mortality rate predicted by the parametric models fell below that of the general population at about 18 years. The impact on the ICER was marginal - approximately £1,500. However, to address this, a cap on the mortality rate has now been included in the amended model, which ensures that, at a minimum, the mortality rate estimated from the OS survival model reflects the general population with a starting age of 63, which represents the mean age of the CheckMate 017 study population. This amendment now corrects for any clinical inconsistent estimates of mortality rates of the parametric

models versus the general population. In addition, the correction for mortality rates was supported by the clinical advisors within the first ACD meeting, who expressed that nivolumab has the potential for long-term survival benefit and could potentially lead to a return to baseline mortality rates for a subset of patients -that is, a mortality risk equivalent to an age-matched member of general population.

Furthermore, as done in the original submission, the predicted OS beyond the latest available clinical dataset (18-month) was validated with longer term (4-year) nivolumab data within NSCLC to ensure the extrapolations predicted by the parametric models were clinically plausible. Specifically, the CheckMate 003 dataset was utilised – this was a Phase 1b dose-escalation study evaluating the safety of nivolumab as a single agent in previously treated patients with advanced melanoma (n=107), NSCLC (n=129), renal cell carcinoma (n=34), castration-resistant prostate cancer (n=17) or colorectal cancer (n=19). The trial population included patients with advanced (non-resectable), or recurrent cancer and for which no alternative, curative standard exists and who had at least 1 and up to 5 prior systemic therapies for advanced/recurrent disease. 4-year OS follow-up specific to the advanced NSCLC cohort was used for the validation of the parametric models.

It is considered that the Checkmate 003 dataset is a strong source of validation for a number of reasons, specifically:

- This dataset reflects the longest term survival data for advanced NSCLC patients on nivolumab
- The survival rates measured from the Checkmate 003 study were comparable to those measured in CheckMate 017 at 6-months, 12-months, and 18-months 66% vs. 64% , 42% vs. 42%, 31% vs.28% providing evidence that the two trials even with differing eligibility criteria show similar survival profiles

Figure 1 below shows a graphical comparison of the longest term follow-up for nivolumab OS – specifically it compares the 18-month Checkmate 017, 4-year CheckMate 003 data, log-logistic extrapolation based on 18 month data, and the ERG approach of extrapolation using KM data plus an exponential function after 40 weeks applied to both the 12-month and 18-month datasets.

Since BMS's revised log-logistic function is based on an additional 6-months of follow-up data, is adjusted for baseline mortality rates, and reflects the longest nivolumab data available, we ask the committee that the log-logistic model for OS extrapolation be considered as the base-case. It should also be noted that the revised log-logistic model is more conservative than the original model submitted to NICE using the 12-month data from CheckMate 017. In the original model, the mean OS for nivolumab and docetaxel was 27.2 months and 11.5 months, respectively. In the revised model, the mean OS for nivolumab and docetaxel is 25.4 months and 11.5 months, respectively.

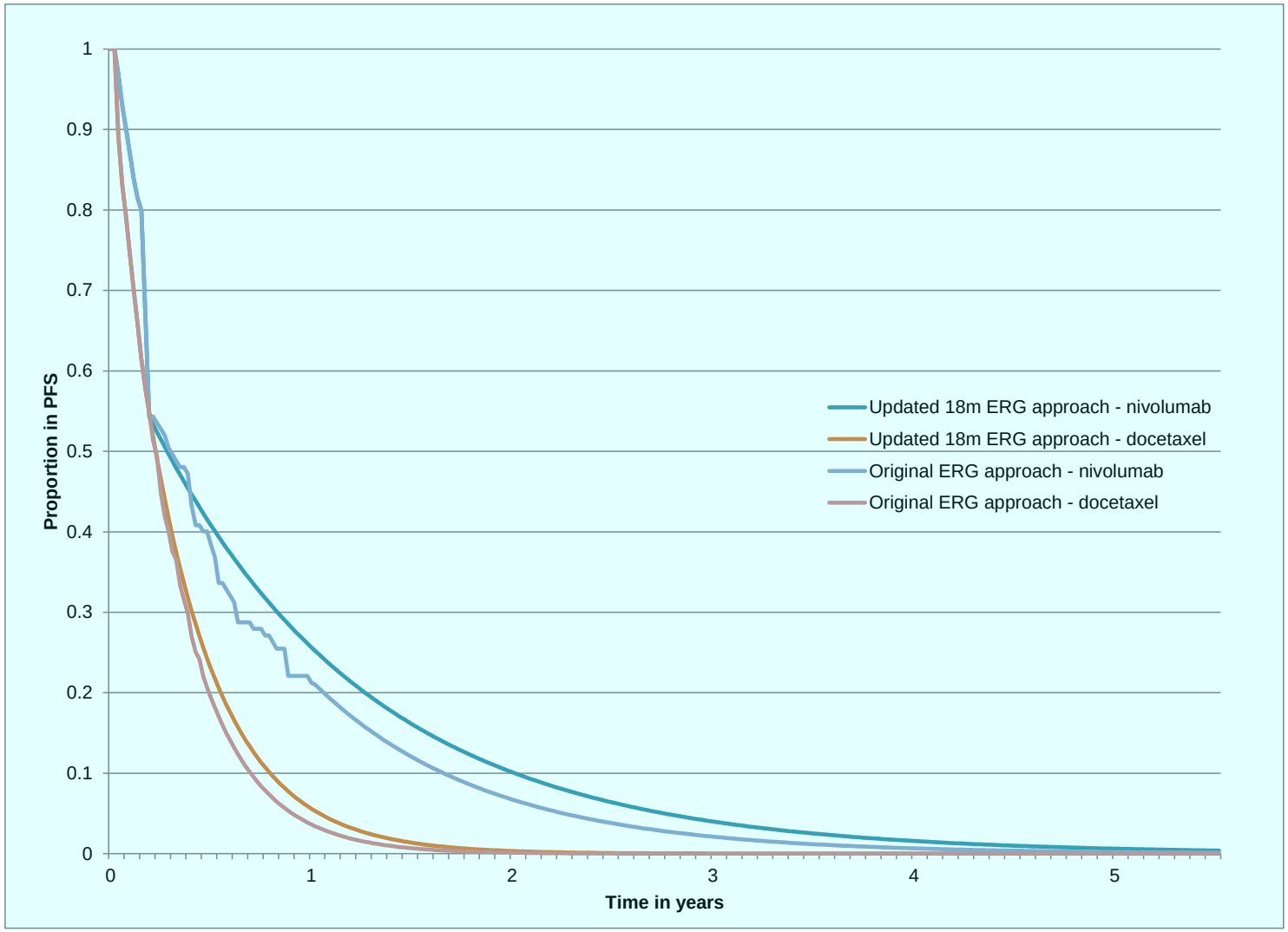
Figure 1: Long-term overall survival of patients on nivolumab

Progression-free survival:

A key limitation of the approach proposed by the ERG for progression-free survival (PFS) extrapolation, which was considered by the committee, was that it was not based on the additional data provided to the Institute during the response to the clarification questions. Specifically, 18-month PFS data from CheckMate 017 was provided in order to facilitate the ERG extrapolation approach of using KM data up to 2.2 months followed by an exponential function. Upon review, it appears that only the 12-month data was considered. Figure 2 below shows a comparison of using KM data up to 2.2 months followed by an exponential function from the original ERG model versus the revised analysis undertaken with the 18-month data set. It is evident from Figure 2 that the original ERG model under predicts the PFS benefit for both docetaxel and nivolumab with a greater difference observed in the nivolumab arm.

Application of the ERG approach for PFS extrapolation in the original model submitted by BMS to the Institute yields an ICER versus docetaxel of £68,912 – assuming no other amendments suggested by the ERG are accepted (only "Mod_4" = ERG PFS projections). In the same model, if the ERG PFS projection is updated with the actual 18-month data as outlined in Figure 2 below, the ICER increases to £77,686. In the revised model being submitted to NICE in response to the ACD, which contains the changes outlined in the ACD response, the ERG approach for PFS extrapolation was updated using 18-month data, resulting in a revised base case ICER of £91,870. Though the ICER increases with the use of the 18-month PFS data, in order to ensure the model reflects the most recent data cut of nivolumab, the revised company model has been amended with the 18-month dataset using the ERG approach of KM data up to 2.2 months, followed by an exponential function.

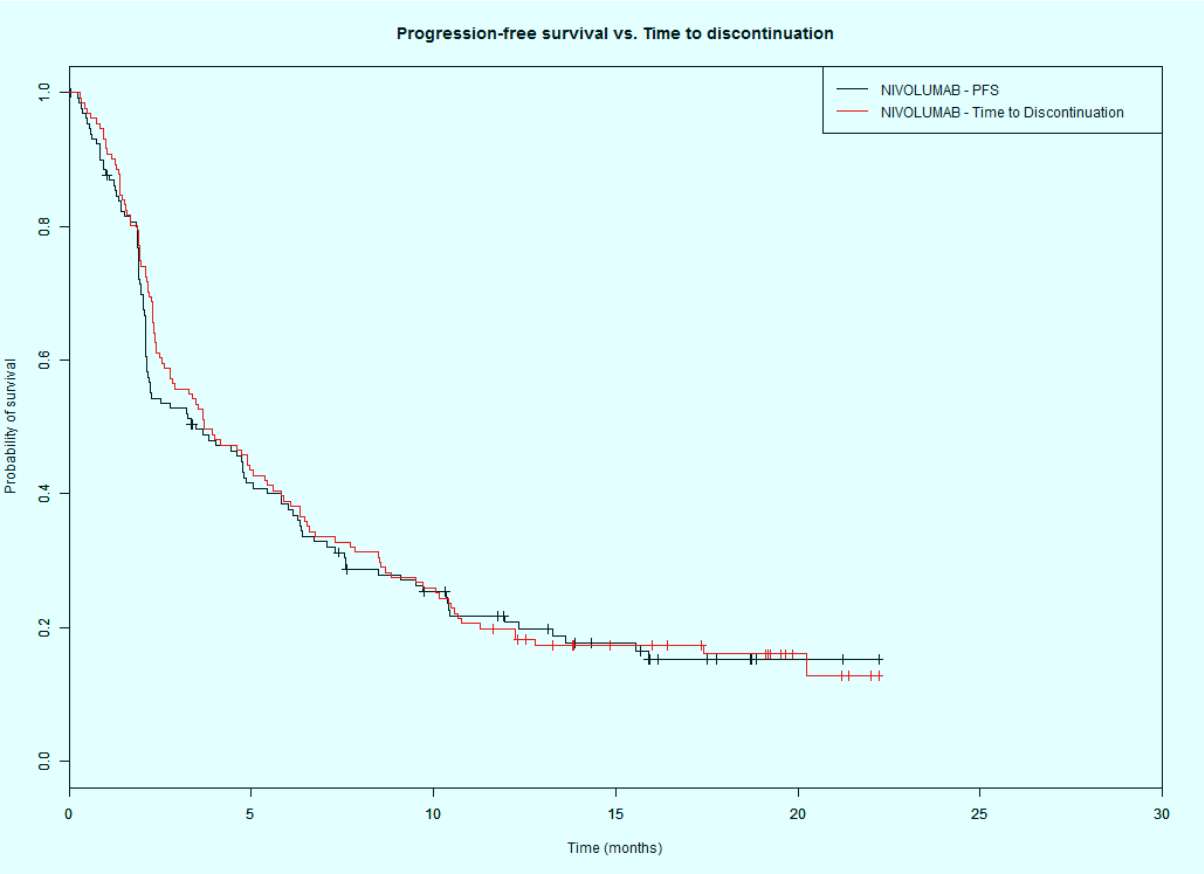
Figure 2: Extrapolation of PFS as per the ERG approach



It was stated within the ACD document that if PFS were to be underestimated the ICER would be higher (Section 4.7, page 19: "The Committee observed that decreasing the progression-free survival gain associated with nivolumab [compared with docetaxel] led to a decrease in the incremental cost-effectiveness ratio (ICER); consequently, it was aware that if the company's concern was correct and the ERG had underestimated the progression-free survival gain, the ICER would be higher than predicted by the ERG."). Though this is consistent with the analysis presented above, it is important to note that the greater PFS benefit captured by the revised analysis means that the model is more accurately capturing the subset of nivolumab patients who continue to experience a durable response to nivolumab. As these patients are not progressing, it can be expected that this will have an impact on OS and therefore a greater incremental OS may also be expected. In fact, it may be expected clinically that patients with stable disease, in addition to those with a complete or partial response, will also contribute to longer term OS. In addition, a greater incremental PFS benefit implies that the model is less dependent on post-progression survival, which was discussed by the ERG and committee. In light of this, it is recommended that the model implements the revised PFS analysis as the base case.

The ERG also expressed concern with regard to the use of PFS rather than time to discontinuation (TTD) to extrapolate the proportion of patients in the progression-free health state. In the Checkmate 017 study, PFS and TTD were compared for nivolumab patients (Figure 3). As outlined in Figure 3 that PFS and TTD for nivolumab are almost identical; therefore, it is assumed that PFS is an appropriate proxy for TTD, and the model is not sensitive to which source of data is used to predict the proportion of patients on treatment for both costs and QALYs. It should be noted that in the ERG amendments it was suggested that using PFS instead of TTD would increase the ICER by approximately £20,000 (scenario R8 of the ERG report on page 101). However, in this scenario the ERG assumed one distribution for treatment costs and a different distribution for PFS QALYs. This choice in differing distribution choice for costs and QALYs explains why scenario R8 has a significant decrease in treatment costs with no change in treatment QALYs in comparison to the base-case scenario. That result is because KM data followed by an exponential function was used to model treatment costs, and a dependent 2-spline hazards model was used for PFS QALYs. Considering the similarities between TTD and PFS it is not methodologically appropriate to use a different distribution to model costs in comparison to pre-progression QALYs.

Figure 3: Nivolumab PFS vs. TTD from Checkmate 017



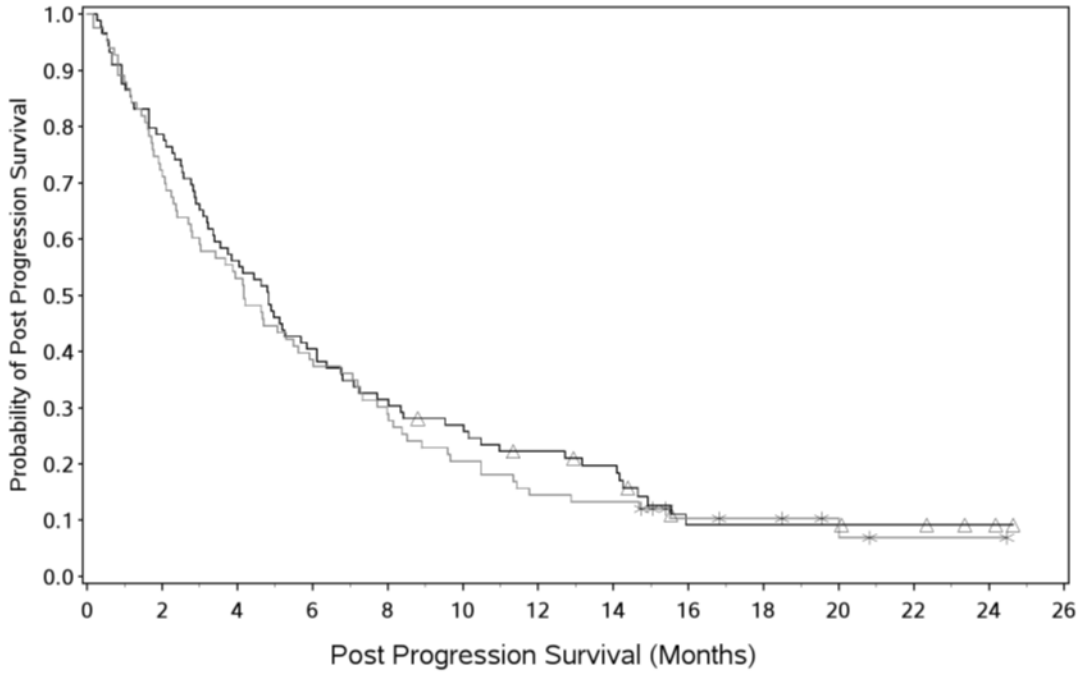
Post Progression survival and survival projections (section 3.15)

In the company model, Overall Survival benefit in patients treated with nivolumab is accrued when patients are in both the progression free (PFS) and progressed disease (PD) states. The committee have expressed concern about the clinical validity of this.

The committee cite Figure 7 from the ERG's assessment report, which was provided by the company in response to the clarification questions. Figure 7 in the ERG report is a Kaplan-Meier plot of a Post Progression Survival (PPS) analysis.

This analysis takes patients who were treated with nivolumab and docetaxel and have transitioned to the PD state at the time of analysis and compares their survival from the time of progression. Figure 7 is reproduced below.

Figure 7 from the ERG report: CheckMate-017 Kaplan-Meier PPS plot (30th July 2015 data cut, using revised censoring algorithm).



Number of Subjects at Risk

NIVOLUMAB 3 mg/kg	89	70	50	36	28	23	18	15	5	5	5	4	2	0
DOCETAXEL	83	60	44	32	24	17	12	11	6	5	3	1	1	0

NIVOLUMAB 3 mg/kg (events: 78/89), median and 95% CI: 4.83 (3.35, 6.11)
DOCETAXEL (events: 75/83), median and 95% CI: 4.17 (2.79, 5.91)

Note that in the ERG report numbers of patients at risk were not included, though these were part of the company submission. There are included above.

The ERG assert that Figure 7 demonstrates no apparent difference in PPS between nivolumab and docetaxel, and hence that the company's model over estimates the survival benefit of nivolumab.

Criticisms of Figure 7 and Post Progression Survival (PPS) Analysis

There are significant concerns with the ERGs approach in analysing PPS, and the PPS survival function cannot be interpreted.

Selection Bias

The patients selected for the PPS analysis are a sub-set of patients who had progressed at the time of follow-up (i.e. when the analysis was performed). This approach selects a group of patients who are not typical of the patients randomized at the start of the trial, as patients with the best prognosis are likely to have not progressed and hence remain in the PFS health state and are not part of the PPS analysis. Analysis of PPS in this way is therefore subject to selection bias in both the nivolumab and docetexel arms.

The magnitude of the underestimation of survival caused by this bias is more significant in nivolumab arm than the docetaxel arm, because more patients in the nivolumab arm are progression free at the time of analysis (15% (n=19 of 135) of nivolumab treated patients were still in PFS at the 18m database lock, in comparison to almost 0% in docetaxel (n=1 of 137)). Hence the nivolumab arm PPS will be underestimated by more than the docetaxel arm, resulting in an underestimate of the difference between nivolumab and docetaxel's PPS.

The selection bias can be analysed in terms of the response characteristics of patients in the PFS and PD states at the time of the 18 month PPS analysis in the nivolumab and docetaxel arms. The Best Overall Response (BOR) for the nivolumab patients in PFS was a either complete or partial response (CR or PR) – 89%, 17 of the 19 patients, whereas there was only one patient remaining in PFS in the docetaxel arm, who had a BOR of PR. In comparison, the BOR of those who had progressed was predominantly stable disease (SD) or progressive disease (PD) – 91% (SD = 28/89 patients, PD = 53/89 patients). The BOR in the PD and PFS nivolumab groups at the time of the PPS analysis are therefore markedly different, demonstrating the selection bias inherent in the PPS analysis. In the docetaxel arm, more than half of the patients who had progressed had a BOR of PD – 54% (PD = 45/83 patients, SD = 32/83 patients).

A recent FDA article which examined the patient level data from 14 trials in NSCLC from 2003 to 2013[1] showed that responders have a statistically significant OS vs. non-responders – with a HR of 0.40 (CI -0.38-0.43). In the CheckMate 017 study, 28 patients received treatment beyond progression (as per RECIST criteria Version 1.1), and of these, nine patients continued to benefit from treatment beyond disease progression and were termed 'non-conventional' benefiters (6.7% of the overall study population; presented in Section 4.7 within the original NICE submission); therefore, the relationship between stable disease and overall survival benefit in patients receiving nivolumab may be underestimated. This provides evidence that the patients still responding on nivolumab at 18 months have a different survival profile to those patients who have progressed and for the PPS analysis, presented in Figure 7, and hence substantiates the assertion of a significant selection bias.

Duration of follow up

The PPS analysis is significantly limited by the duration of follow up and the number of patients at risk. The minimum follow up in the study at the July database lock was approximately 18 months, and very few patients were at risk for PPS beyond 14 months (the number of patients at risk can be seen on Figure 7, above). Furthermore, 30 Nivolumab patients didn't influence the PPS analysis at all (either because they remained PFS or had not died) whereas only 15 docetaxel patients had not progressed or died. Taken as a whole, these observations indicate that there is insufficient data and follow for the PPS analysis to be meaningfully performed.

[1] Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol 2015; 33(9): 1008-1014.

The longest follow-up available for nivolumab is from CheckMate 003, as discussed in the company submission. The OS and PFS from this study are demonstrated in Figure 4.

There is an apparent plateau of the OS curve at a higher level than PFS, indicating long-term survival of some nivolumab patients who experience progression according to RECIST 1.1 criteria, and supporting a survival benefit for patients after progression.

Figure 4: Survival (OS and PFS) in the CheckMate 003 study

The "Week 12" assessment refers to assessments at Week 12 for patients remaining on treatment; post-treatment assessments are described as follow-up assessments number 1 and 2. For example, for Nivolumab, 71 patients remained on treatment at Week 12 and 50 patients completed the EQ-5D at the Week 12 on-treatment assessment, which is a completion rate of 70.4% (BMS data on file available on request); the ERG describes compliance at Week 12 as 32%, dividing the assessments by all randomized subjects. Therefore, the potential for selection bias in the on-treatment assessments is actually much lower than as was stated by the ERG.

Scenario analyses (exploratory):

The Committee noted the EQ-5D results were influenced with selection bias, and may not be representative of the wider population. To address this limitation with the data, additional analyses were performed. Firstly, instead of averaging the utility values for all patients at every time point, only a single average utility value was included for each patient for a certain health state (i.e., all recorded utility values for a single patient were averaged across all time points for a certain health state to yield a single value, as exemplified in Table 2). The average of these averages was then calculated to give 0.692 and 0.594 for progression-free and progressed-

disease health states, respectively. This method reduced the influence of the later results where drop-out was observed.

In addition, time-dependent estimates were generated, to evaluate the utility values for each health state at every time point. Looking at the data across all time points, the time point with the largest number of PF assessments was at baseline (averaging these gives a utility value of 0.671), and the time point with the largest number of PD assessments was week 12 (averaging these gives a utility value of 0.537). As the "averages of averages" approach utilises all patient level data available from the trial, it is the recommended scenario analysis in comparison to the time-dependent values, which only uses a subset of the data at a particular time point.

Table 2: Example of calculation of health states using "average of averages":

PF assessments	**EQ-5D value – UK index**				
	1st recorded value in health state	**2nd recorded value in health state**	**3rd recorded value in health state**	**4th recorded value in health state**	**Avg per patient**
Patient 1	0.70	0.75	0.80	0.85	(0.70+0.75+0.80+0.85)/4= 0.78
Patient 2	0.70	0.70	Not available	Not available	(0.7+0.7)/2= 0.70
…	…	…	…	…	…
Average PF health state value ("average of average)	(0.78+0.70)/2=0.74				
Original method of averaging the utility values for all patients at every time point	(0.7+0.75+0.8+0.85+0.7+0.7)/6 = 0.75				

The Committee also noted that the utility values presented were higher than corresponding utilities in other lung cancer appraisals. However, the utility values observed in CheckMate 017 (0.750 and 0.592 for progression-free and progressed-disease health states, respectively) are robust and aligned with those observed in CheckMate 057, the Phase III trial of nivolumab in non-squamous patients with NSCLC (0.739 and 0.688 for progression-free and progressed-disease health states, respectively). Additional information on the CheckMate 057 utility values can be made available on request.

Cost effectiveness results and summary

We would like to ensure the committee has an updated assessment of cost effectiveness available, as the basis for its decision making. We have therefore presented updates analyses using the latest data available from study CheckMate 017 in addition to changes outlined below.

BMS have adopted some of the parameters and assumptions suggested by the ERG applied to inform the cost effectiveness model, namely, the following:

- The model is structured so that neither OS nor PFS/TTD can be above the UK all-cause mortality rate for a cohort of patients.
- Treatment duration should be modelled using KM data up to 2.2 months followed by an exponential function due to the fact that a parametric model for the entire dataset will be heavily influenced by the steep drop in the PFS/TTD curves seen at 9 weeks, as this was the first assessment in the trial
- The cost per dose of nivolumab and comparators is based on the weight and body surface area calculator provided by the ERG during the review of the nivolumab in squamous NSCLC model.
- Revision to second and third line drug costs.
- Drug cost being applied at the start of cycle.

As discussed above, BMS do not agree with the ERG extrapolation of overall survival (OS) to inform the CE modelling. Moreover, BMS consider the quality of life data collected in CheckMate 017 to be robust and most appropriate for this appraisal, we also note this is in line with the NICE reference case.

Revised base case analysis

The revised base case analysis, assuming that patients are treated to progression, is provided in Table 5 and is based on the log-logistic curve for OS, the ERG approach for PFS (using 18m data), as discussed above (KM data up to 2.2 months followed by an exponential function), and the adopted changes from the ERG listed above.

In the revised base case, nivolumab generates 0.68 incremental QALYs and 1.16 incremental life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The ICER is £91,870 per QALY gained (Table 5).

Table 3: Revised base case - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
Disease	1.22	0.59	0.63	0.63	93.2%
AE disutility	-0.01	-0.05	0.05	0.05	6.8%
Total	1.22	0.54	0.68	0.68	100%

Abbreviations: AE = Adverse Event; QALY = Quality-Adjusted Life Year

Table 4: Revised base case - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
Disease	17,694	10,639	7,056	7,056	11.4%
Drug acquisition cost	51,489	590	50,898	50,898	82.11%
Administration cost	5,592	1,349	4,243	4,243	6.8%
Monitoring cost	2,129	1,236	893	893	1.4%
AEs	228	1,304	-1,076	-1,076	-1.7%
Total treatment cost	77,132	15,118	62,014	62,014	100%

Abbreviations: AE = Adverse Event

Table 5: Revised base case results

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	77,132	2.12	1.22	62,014	1.16	0.68	91,870
Docetaxel	15,118	0.96	0.54				

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; LYG = Life-Years Gained; QALYs = Quality-Adjusted Life Years

Scenario analysis – updated EQ-5D analysis using "averages of averages"

A scenario analysis was performed using utility values derived from the CheckMate 017 study using the "averages of averages" method discussed above (0.692 and 0.594 for progression-free and progressed-disease health states, respectively). Assuming that patients are treated to progression, and using the log-logistic curve for OS, the ERG approach for PFS (using 18m data) as discussed above (KM data up to 2.2 months followed by an exponential function), and the adopted changes from the ERG listed above, the results of this scenario are presented in Table 8.

In this scenario, nivolumab generates 0.65 incremental QALYs and 1.16 incremental life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The ICER is £94,933 per QALY gained (Table 8).

Table 6: Scenario 1 - Summary of QALY gain using "averages of averages" EQ-5D data

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
Disease	0.45	0.29	0.61	0.61	92.9%
AE disutility	-0.01	-0.05	0.05	0.05	7.1%
Total	1.07	0.49	0.65	0.65	100%

Abbreviations: AE = Adverse Event; QALY = Quality-Adjusted Life Year

Table 7: Scenario 1 - Summary of costs using "averages of averages" EQ-5D data

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
Disease	17,694	10,639	7,056	7,056	11.4%
Drug acquisition cost	51,489	590	50,898	50,898	82.11%
Administration cost	5,592	1,349	4,243	4,243	6.8%
Monitoring cost	2,129	1,236	893	893	1.4%
AEs	228	1,304	-1,076	-1,076	-1.7%
Total treatment cost	77,132	15,118	62,014	62,014	100%

Abbreviations: AE = Adverse Event

Table 8: Scenario analysis – using "averages of averages" EQ-5D data

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	77,132	2.12	1.17	62,014	1.16	0.65	94,933
Docetaxel	15,118	0.96	0.52				

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; LYG = Life-Years Gained; QALYs = Quality-Adjusted Life Years

Scenario analysis – 1 year treatment stopping rule

In a scenario with a 1 year treatment stopping rule, using the same settings as the revised base case, nivolumab generates 0.68 incremental QALYs and 1.16 incremental life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The ICER is £61,555 per QALY gained (Table 11).

Table 9: Scenario 2 - 1 year treatment stopping rule

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
Disease	1.22	0.59	0.63	0.63	93.2%
AE disutility	-0.01	-0.05	0.05	0.05	6.8%
Total	1.22	0.54	0.68	0.68	100%

Abbreviations: AE = Adverse Event; QALY = Quality-Adjusted Life Year

Table 10: Scenario 2 - 1 year treatment stopping rule

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
Disease	17,694	10,639	7,056	7,056	17.0%
Drug acquisition cost	33,404	590	32,814	32,814	79.0%
Administration cost	3,728	1,349	2,379	2,379	5.7%
Monitoring cost	1,614	1,236	378	378	0.9%
AEs	228	1,304	-1,076	-1,076	-2.6%
Total treatment cost	56,669	15,118	41,551	41,551	100%

Abbreviations: AE = Adverse Event

Table 11: Scenario 2 analysis – 1 year treatment stopping rule

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	56,669	2.12	1.12	41,551	1.16	0.68	61,555
Docetaxel	15,118	0.96	0.54				

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; LYG = Life-Years Gained; QALYs = Quality-Adjusted Life Years

Scenario analysis – 2 year treatment stopping rule

In a scenario with a 2 year treatment stopping rule, using the same settings as the revised base case, nivolumab generates 0.68 incremental QALYs and 1.16 incremental life years compared with docetaxel and the nivolumab-treated cohort has higher total lifetime costs. The ICER is £80,306 per QALY gained (Table 14).

Table 12: Scenario 3 – 2 year treatment stopping rule

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
Disease	1.22	0.59	0.63	0.63	93.2%
AE disutility	-0.01	-0.05	0.05	0.05	6.8%
Total	1.22	0.54	0.68	0.68	100%

Abbreviations: AE = Adverse Event; QALY = Quality-Adjusted Life Year

Table 13: Scenario 3 – 2 year treatment stopping rule

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
Disease	17,694	10,639	7,056	7,056	13.0%
Drug acquisition cost	44,590	590	44,000	44,000	81.2%
Administration cost	4,881	1,349	3,532	3,532	6.5%
Monitoring cost	1,932	1,236	696	696	1.3%
AEs	228	1,304	-1,076	-1,076	-2.0%
Total treatment cost	69,326	15,118	54,208	54,208	100%

Abbreviations: AE = Adverse Event

Table 14: Scenario 3 analysis – 2 year treatment stopping rule

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	69,326	2.12	1.22	54,208	1.16	0.68	80,306
Docetaxel	15,118	0.96	0.54				

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; LYG = Life-Years Gained; QALYs = Quality-Adjusted Life Years

ADDENDUM 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer [ID811]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/05

Completed 8th February 2016

Contains commercial in confidence data

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Bristol-Myers Squibb (BMS) response to the Appraisal Consultation Document (ACD) for nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)

Evidence Review Group (ERG) commentary on issues raised

1 Long-term mortality projection

The ERG highlighted that the parametric function employed by the company (BMS) to project future survival (Log-logistic) resulted in indefinitely reducing mortality rates throughout patients' remaining lifetimes. In particular, at some time for both nivolumab and the comparator treatment, this survival model requires that mortality falls below the level of an age-sex adjusted cohort of the general population, implying that treatment with either agent confers an indefinite benefit, ultimately yielding better long-term prognosis than patients who have not suffered from NSCLC.

The company responded by introducing a model amendment to prevent mortality rates falling below the level in the UK Life Tables. This change does not address the fundamental problem, that the log-logistic curve can never accurately represent a human population which in the long-term always experiences steadily increasing mortality hazards with advancing age. Put simply, the use of this and similar parametric functions with 'long-tails' and ever decreasing mortality rates is frequently implausible for modelling long-term survival. An arbitrary cap on mortality does not address this methodological weakness.

2 Progression-free survival (PFS) and time to treatment discontinuation (TTD)

The company appears to have misinterpreted the ERG's view of the appropriate use of PFS and TTD in the economic model. The ERG considers that PFS data should be used to determine the progress of patients out of the responder/stable disease health state (PFS) and into the progressive disease state (post-progression survival, PPS), so that appropriate health state costs and utilities are applied to those in the respective states. However, the costs of treatment (acquisition, administration and monitoring) should be based on TTD data since over time patients may cease therapy prematurely (prior to disease progression) for various reasons; in addition, patients in the nivolumab arm were permitted to continue treatment beyond disease progression if the clinician considered that some additional benefit might accrue. Without use of TTD, the cost of treatment can be both over- or understated if PFS is used to estimate both costs and health state occupancy.

3 Survival analyses and clarification data

The company suggests that the ERG did not make use of the latest trial results requested through clarification requests when estimating PFS trends (and by implication perhaps other survival models). This is not the case, though the pattern of events is rather more complex:

- ERG requested new analyses of the trial results for overall survival (OS), PFS, TTD and PPS
- At the response due date (25th September 2015), BMS stated that this part of the clarification letter response was ongoing and would be available in a week
- A further response document was provided (dated 30th September 2015) which repeated the statement that work was on-going on these requests. However, a set of survival analysis charts based on the latest July 2015 data cut were provided covering the ERG requests, but without the detailed figures requested.

At this point a full working week had been lost for ERG analysts to work on the missing evidence, with the prospect of still more delay. A decision was therefore taken by the ERG to digitise the survival charts available so that some progress could be made to inform the revision of the company model in time for inclusion of results in the ERG report.

Subsequently, a third company response (dated 2nd October 2015) was received in the form of a spreadsheet containing detailed numeric data. By this time digitisation of the available charts was already complete, and modelling of survival trends was at an advanced stage. The new data appeared to match the digitised curves quite closely, and therefore it was considered appropriate to proceed to populate a revised version of the company model with the data already to hand (presumed to be from the same analyses of the clinical trial data as provided later in detail).

The exception to this was PPS, where the ERG needed to create a replica dataset at the level of individual patient records in order to test the similarity of PPS in the two trial arms (using the Log-rank test). This required use of the detailed spreadsheet numbers. It also allowed modelling of a common pooled PPS survival trend, when the Log-rank test confirmed that there was no significant difference in PPS attributable to randomised treatment.

Since BMS have repeated the claim that the ERG did not use the July data provided, the two sources of evidence sets available to the ERG (survival charts, and spreadsheet figures) have been re-examined carefully. It appears that for each analysis there are important discrepancies present, suggesting that the survival charts first provided may have been subsequently superseded by a later analysis.

Therefore the ERG has now repeated its modelling of OS, PFS and TTD using the patient-

level figures and produced improved projections for use in the company model.

4 Post-progression survival

The company challenges the ERG finding that the evidence from CheckMate 017 does not currently provide evidence of any survival advantage beyond disease progression.

Firstly, it is suggested that the PPS analysis is flawed by **selection bias**.

The ERG considers the selection bias argument to be unfounded. It is always the case that patients will progress at different times in the arms of any trial due to differential efficacy between patients. The issue here is whether the prognosis for progressing patients at the time of progression is the same or different in the two trial arms; the default assumption is that 'progressive disease' means that the active treatment has failed, and that the natural history of the disease has reasserted itself.

If it is believed that nivolumab continues to show significant active survival benefit beyond disease progression, then this can only be verified by examination of the PPS trial results. In this case the PPS data fail to show any significant difference between the trial arms (Log-rank test p = 0.850). Therefore the natural inference is that survival benefit is confined to the pre-progression state, augmented only by any differential mortality seen at the time of progression.

Secondly, it is suggested that there is **inadequate follow-up** in the trial beyond disease progression to yield meaningful results.

Of course it would be ideal to have longer follow-up of patients, but the ERG does not consider that there is any sound reason to dismiss these findings. There are approximately equal numbers of patients included in the arms of the PPS analysis (89 vs 83), and the maximum follow-up (last patients still at risk) was the same in both arms (over 24 months).

Finally, the company refers to survival results from **another clinical trial** (CheckMate 003).

However, this single arm trial does not address the central finding of the ERG's analysis – that there is no relative difference in survival beyond disease progression due to treatment with nivolumab – since there is no comparator in CheckMate 003.

In summary, the company document states: "It is expected the PPS analysis will demonstrate diverging post progression survival in the nivolumab and docetaxel arms."

The ERG considers that it would require a very large differential in PPS to be present in the patients remaining on treatment in CheckMate 017 to show a significant overall PPS advantage, and that estimates of survival gain in this appraisal should be based on the clinical trial results now available, rather than on speculative aspirations of what might be

shown when follow-up is complete.

5 Quality of life

In response to ERG concerns that the EuroQol-5 dimension (EQ-5D) questionnaire data in the CheckMate 017 trial were seriously biased by the selective participation of fitter patients, the company has proposed an alternative method for deriving estimates of health state utilities. This involves creating separate averages of all EQ-5D estimates obtained for each individual patient, and then averaging these values over all patients with submitted data. In effect this involves weighting individual utility estimates inversely depending on how many times they completed the EQ-5D form, described as 'average of averages'.

This novel approach to data manipulation does indeed have the effect of reducing the company's original health state utility estimates to some extent, but the offered justification for this unconventional mathematical manoeuvre lacks obvious merit.

The ERG has therefore revisited the health state utility estimates previously reported in view of the Appraisal Committee's (AC's) dissatisfaction with any of the options presented by the company or ERG.

Progression-free survival (PFS). The decision model is structured on the assumption of a stable utility associated with the PFS health state. However, the ERG report demonstrated clearly that the CheckMate 017 trial data were not consistent with this assumption. In view of the strongly increasing trend of EQ-5D utility estimates over time in the trial in both treatment arms, the ERG has instead selected only the early trial results from the period when the estimated mean utility lies below the value of the UK EQ-5D norm adjusted to the age distribution of the trial population. This limits analysis to patient responses less than 10 weeks after randomisation, and includes just over 50% of the available trial data. This approach yields very similar utility values (0.702 for nivolumab patients, 0.688 for docetaxel patients and 0.693 overall), which fall between the previous non-trial-based ERG estimate (0.65) and the age-adjusted UK population norm (0.80).

***Post-progression survival (PPS)*.** A Dutch clinical trial by van den Hout et al (2006) has been identified which studied alternative modes for delivering palliative radiotherapy to advanced NSCLC patients receiving only supportive care. Firstly, EQ-5D utility values using the UK valuation set were plotted over time from randomisation for 52 weeks, indicating generally steady results over time that are consistent with the BMS model assumption of a single utility value whilst in the PPS state.

However, an additional analysis was presented based on considering EQ-5D values by the time prior to patient death. This shows that an extended period of utility stability (12 to 6 months prior to death) is followed by an accelerating decline in EQ-5D utility to values close

to zero as death approaches, especially in the last 3 months of life. This additional substantial disutility associated with the terminal phase of care is not included in the company model, so that all quality adjusted life years (QALYs) attributed to patients are overestimated at the end of life.

The ERG has used data from the Dutch trial to re-estimate the stable PPS mean utility in both treatment arms as 0.545. In addition, the total additional disutility associated with the terminal care phase has been calculated. Since the company model is not structured to accommodate the latter effect, an adjustment has been applied to the stable PPS value which effectively spreads the terminal disutility over the mean duration of PPS in CheckMate 017. This reduces the net EQ-5D utility estimate to 0.460, slightly greater than original ERG value (0.43), but lower than the original company value (0.592) or revised alternatives (0.594 or 0.537).

6 Impact of additional model adjustments to cost effectiveness results

In the ERG report, nine issues were identified as affecting estimates of the cost effectiveness of nivolumab versus docetaxel in treating patients suffering from advanced squamous NSCLC after previous chemotherapy. The views of the AC on these issues and the related ERG proposed model amendments (R1 to R9) were detailed in the ACD document, and are summarised in Table A.

Table A: Summary of AC assessment of issues identified in the ERG report

Issue	ERG amendment	AC decision
PFS projection	R1 long-term exponential model	Accepted
OS projection	R2 long-term exponential model	Accepted
Treatment costs	R3 revised individual costing	Accepted
Later treatment costs	R4 revised individual costing	Accepted
Treatment administration costs	R5 and R7 same unit cost for each treatment, occurring at the start of each cycle	Accepted
Limit docetaxel	R6 restrict treatment cost to 4 cycles	Not accepted
Treatment duration	R8 use TTD trial results for costing treatments (not PFS)	Accepted
Utility values	R9 use values from Standard Gamble study	Neither BMS trial values nor ERG values accepted

AC=Appraisal Committee; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation

In the light of the views previously expressed by the AC, and of the specific revised analyses described above, the ERG has updated the cost effectiveness results previously shown in Table 39 of the ERG report, as Table B below. Compared with the original company base case scenario, the effect of applying all of the approved ERG model amendments after the updating of evidence as described above, is to increase the estimated incremental cost effectiveness ratio (ICER) from £85,590 per QALY gained to £154,352 per QALY gained.

Table B Cost effectiveness results (nivolumab 3mg/kg Q2W vs docetaxel 75mg/m^2 Q3W): Updated ERG revisions to original company base case comparison (using list prices for nivolumab and docetaxel)

Model scenario ERG revision	**Nivolumab 3mg/kg Q2W**			**Docetaxel 75mg/m^2 Q3W**			**Incremental**			**ICER**	**ICER**
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
A. Company's base case	**£86,599**	**1.299**	**2.261**	**£21,243**	**0.539**	**0.953**	**+ £65,355**	**+ 0.760**	**+ 1.308**	**£85,950**	-
R1) ERG PFS estimates	£71,219	1.265	2.261	£21,252	0.539	0.953	+ £49,967	+ 0.726	+ 1.308	£68,819	**- £17,131**
R2) ERG OS estimates	£79,958	0.897	1.347	£19,619	0.441	0.750	+ £60,339	+ 0.456	+ 0.597	£132,353	**+ £46,402**
R3) Costs of 2nd line drugs	£85,597	1.299	2.261	£15,742	0.539	0.953	+ £69,854	+ 0.760	+ 1.308	£91,867	**+ £5,916**
R4) Costs of 3rd line drugs	£86,089	1.299	2.261	£20,550	0.539	0.953	+ £65,539	+ 0.760	+ 1.308	£86,192	**+ £241**
R5) Common administration cost	£84,332	1.299	2.261	£21,243	0.539	0.953	+ £63,089	+ 0.760	+ 1.308	£82,970	**- £2,981**
R7) Timing of chemotherapy: drugs given at the start of each cycle	£87,311	1.299	2.261	£21,420	0.539	0.953	+ £65,891	+ 0.760	+ 1.308	£86,654	**+ £704**
R8) Drug costs based on TTD data	£79,153	1.299	2.261	£19,185	0.539	0.953	+ £59,968	+ 0.760	+ 1.308	£78,865	**- £7,086**
R9) Use utilities from Dutch NSCLC trial	£86,599	1.101	2.261	£21,243	0.445	0.953	+ £65,355	+ 0.656	+ 1.308	£99,669	**+ £13,719**
B. ERG revised base case A+R1 to R5, R8, R9	**£69,880**	**0.738**	**1.347**	**£13,000**	**0.369**	**0.750**	**+ £56,880**	**+ 0.369**	**+ 0.597**	**£154,352**	**+ £68,401**

Costs and QALYs discounted; life years undiscounted
BMS= Bristol-Myers Squibb; ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation
Note:
R6 Limiting docetaxel treatment to 4 cycles not accepted by Appraisal Committee
R7 and R8 are not mutually exclusive options as R7 is implicit within the R8 application of TTD estimates

7 Additional Comments on Survival Projection

Correspondence of ERG model with trial data

Figure 1 of the company's response to the ACD for this appraisal presents a comparison between the projective survival model used in the company model to project OS in the nivolumab arm, alongside the ERG's exponential projection and the available Kaplan-Meier data from the CheckMate 017 and CheckMate 003 trials. It is claimed that this demonstrates the superiority of company's log-logistic parametric model in relation to data from both trials.

There are important features of the CheckMate 003 trial which should be considered in this context:

- Published trial results (Gettinger et al 2015) indicate that this single-armed study included all types of NSCLC patients, of which only 54 out of 129 were classed as having squamous cell NSCLC
- The data shown in Figure 1 of the BMS document relate to the whole trial population, not to the squamous subgroup relevant to this appraisal
- After 3 years, only 6 squamous patients and 6 non-squamous patients remained at risk so that there is considerable uncertainty attaching to the survival estimates toward the end of the available follow-up period

In addition the ERG has subsequently updated its projective survival models as outlined above (Section 3). Therefore the ERG has produced an updated version of the company's chart including the longer follow-up data now available for CheckMate 017 for comparison with the updated ERG OS projective model shown below (Figure 1).

It now appears that the ERG model closely matches trial data from both trials to 27 months. Moreover, the ERG model falls within the 95% confidence interval for the Checkmate 003 at 12, 24 and 36 months (as reported in Gettinger et al 2015). **On this basis there is no basis for asserting that the ERG model does not adequately correspond with the CheckMate 017 data, or that it does not match adequately the CheckMate 003 data (notwithstanding that these data are not from the appropriate smaller squamous subgroup which will have even wider confidence limits).**

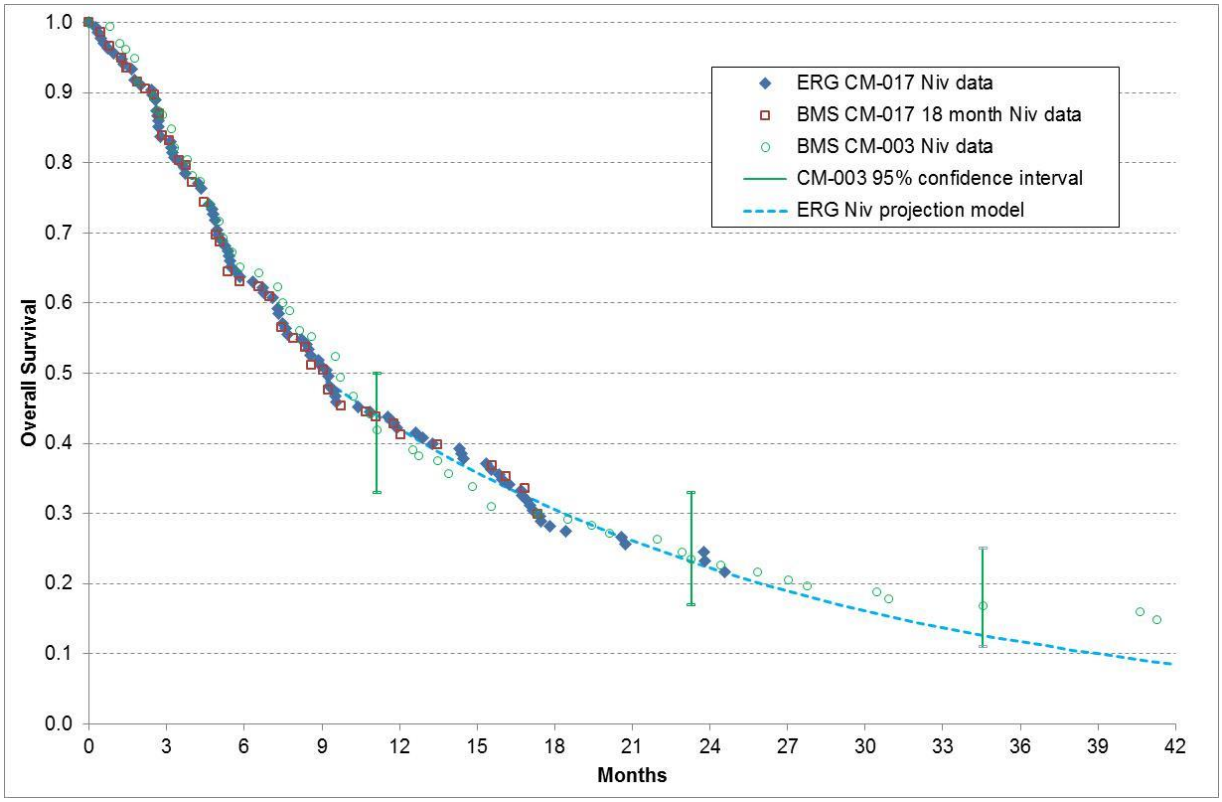


Figure 1: Updated comparison of ERG OS projection model for nivolumab with latest trial Kaplan-Meier results from CheckMate 017 and CheckMate 003.

Modelling the natural history of metastatic NSCLC

The company make reference in their submission to a survival analysis of NSCLC patients included in the Surveillance, Epidemiology, and End Results (SEER) database who were diagnosed with Stage IIIb/IV NSCLC in 1994. Since this preceded the first licensed used of docetaxel in 1996, these data may be considered to represent a population untreated with most currently used chemotherapy agents, except possible some receiving docetaxel as a second-line therapy.

The ERG have analysed these survival results from 5666 patients to consider the survival trend over the full 17 years of reported survival estimates. Figure 2 displays the SEER data together with a model fitted by the ERG, which shows a very close correspondence. The model consists of two elements: a component which involves a very high initial mortality rate, but which reduces rapidly over the first two years eventually tending to zero, combined with a constant lower level mortality rate (equivalent to an exponential survival function).

This can be interpreted as the combination of two distinct patient subgroups:

- The great majority for whom the prognosis is extremely poor measured in months
- A much smaller group subject to a steady average mortality risk of about 10% per year

However, after about 3 years, the first group have almost all died, and the constant risk (exponential survival function) dominates.

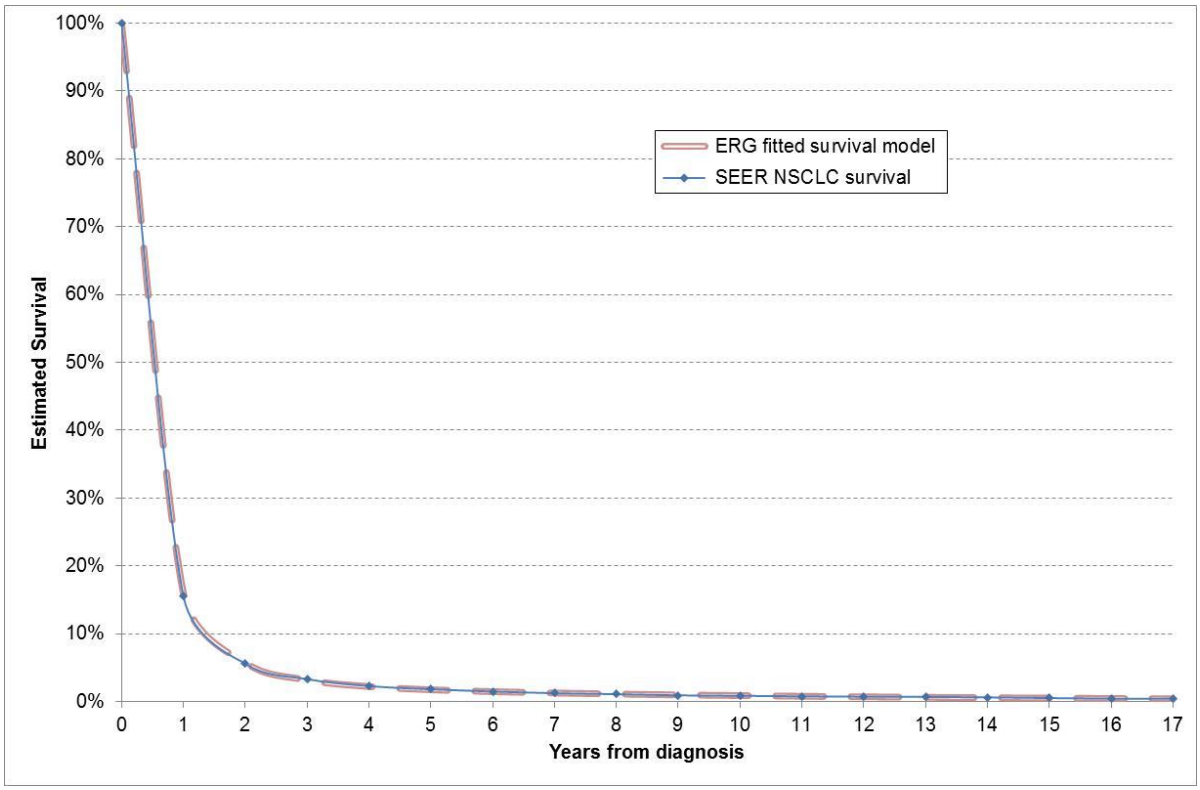


Figure 2: SEER NSCLC survival data from patients diagnosed in 1994 and followed-up to 2011, with ERG fitted parametric model

The ERG therefore concludes that the SEER data support the view that in long-term follow-up of NSCLC trial cohorts, the use of exponential projection functions for survival is fully consistent with real world data, and represents the underlying natural history of the condition. In particular, when all active efficacious interventions are exhausted and patients receive only supportive/palliative care long-term survival can normally be expected to be subject to a Poisson mortality process resulting in an exponential survival trend.

8 References for CheckMate 017 and CheckMate 003

CheckMate 017

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373(2):123-35.

Reckamp K, Spigel D, Rizvi N, Poddubskaya E, West H, Eberhardt W, et al. Phase 3, Global, Randomized Trial (CheckMate 017) of Nivolumab vs docetaxel in advanced squamous (SQ) cell non-small cell lung cancer (NSCLC). 16th World Conference on Lung Cancer. September 6-9; Denver, CO. Abstract 736. 2015.

CheckMate 003

Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol. Epub 2015 Apr 20.

9 Additional reference

Dutch NSCLC trial

van den Hout WB, Kramer GW, Noordijk EM, Leer J-WH. Cost–utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. JNCI 2006; 98(24): 1786-94

Surveillance, Epidemiology, and End Results (SEER) database

Bristol-Myers Squibb. (2010) Long-term and conditional survival estimates for advanced non-small cell lung cancer patients (NSCLC) from the Surveillance, Epidemiology, and End Results (SEER) registry data; 22 June 2010.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

August 2015

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.

Generic Name: Nivolumab

Brand Name: Opdivo®

Disease area: Lung Cancer

Indication: Locally advanced or metastatic squamous non-small cell lung cancer (sqNSCLC) after prior chemotherapy in adults.

Please note that the simple confidential PAS will also apply to all indications for nivolumab but these are not the subject of this appraisal or analysis below. Nivolumab is also currently licensed for as monotherapy or with ipilimumab for advanced unresectable or metastatic melanoma and in advanced renal cell carcinoma after prior therapy.

3.2 Please outline the rationale for developing the patient access scheme. Please describe the type of patient access scheme, as defined by the PPRS.

There are currently limited treatment options available for patients diagnosed with sqNSCLC, previously treated with chemotherapy. No new agents have been licensed for previously treated advanced sqNSCLC for over 10 years. The unmet need is particularly significant for sqNSCLC patients, who typically do not have epithelial growth factor receptor (EGFR) or anaplastic lymphoma receptor tyrosine kinase (ALK) mutations, and hence do not benefit from available targeted agents. Current therapy, docetaxel, has poor response rates and limited efficacy. Erlotinib (an EGFR tyrosine kinase inhibitor [TKI]) offers an alternative treatment option in the second-line setting (given in this context for wild-type patients), but this is under re-review by NICE (ID620). In the third-line setting there are currently no therapies approved by NICE.

Opdivo® provides an unprecedented survival benefit (41% reduction in death compared with standard of care) in patients where no new treatments have been available, a step-change in comparison to therapeutic alternatives.

When the NICE Appraisal Committee's preferred modelling assumptions are used, along with the current list price of nivolumab, the incremental cost-effectiveness ratio (ICER) is higher than NICE's anticipated willingness to pay threshold. BMS is therefore proposing a simple discount scheme to meet NICE cost-effectiveness criteria for England and Wales.

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

The proposed Opdivo® patient access scheme (PAS) will apply to all patients covered by NICE guidance for Opdivo® for locally advanced or metastatic squamous non-small cell lung cancer (sqNSCLC) after prior chemotherapy in adults.

3.4 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.

As noted above, BMS is proposing a simple discount PAS, allowing the drug to meet NICE cost-effectiveness criteria for England and Wales. This would apply to all patients in the population specified.

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

Population	**Proportion of patients**	**Number of patients**	**Reference**
Total NSCLC	N/A	27,300	(Health and Social Care Information Centre 2014)
Patients with stage IIIb/IV NSCLC	N/A	19,138	(Health and Social Care Information Centre 2014)
Squamous NSCLC	36%	6,822	(Powell 2013)
Patients who receive 1st line therapy	25%	1,706	(NICE 2010)
Patients who failed 1st line therapy	50%	**853**	(Sculier 2009)

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

A simple confidential [redacted] discount will be offered for Opdivo®; therefore, no rebates are to be calculated or paid.

3.7 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.

A fixed price (which will not vary with any change to the UK list price) is proposed, if list price is reduced to below the fixed PAS price then this would become the new price point for the PAS.

The proposed discount will be reflected on the original invoice for direct supply of Opdivo® to NHS Trusts. For supply through homecare companies, Bristol-Myers Squibb Pharmaceuticals Ltd will rebate homecare companies the difference between list price and PAS price based on number of Opdivo® packs sold via homecare. The homecare provider will invoice NHS trusts for Opdivo® at the PAS price. We believe this is consistent with existing financial flows within NHS.

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

Not applicable.

3.9 Please provide details of the duration of the scheme.

There are no plans or clauses or circumstances where BMS will withdraw the proposed Opdivo® PAS nationally where the scheme is being operated with normal procurement practices and under standard terms and conditions. BMS will look to consult with stakeholders (including DH and PASLU) on any scheme changes and will participate in any required exit arrangement from the Opdivo® PAS should these be required. In the event of negative NICE advice (i.e. for NICE appraisals ID 811,900), PAS will not apply.

3.10 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?

Not applicable

3.11 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.

PAS agreement form (including terms and conditions): This is where BMS Standard Terms and Conditions will be used for supply of Opdivo®

3.12 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.

Not applicable

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.

Results of the revised model are presented in Section 4.3 below.

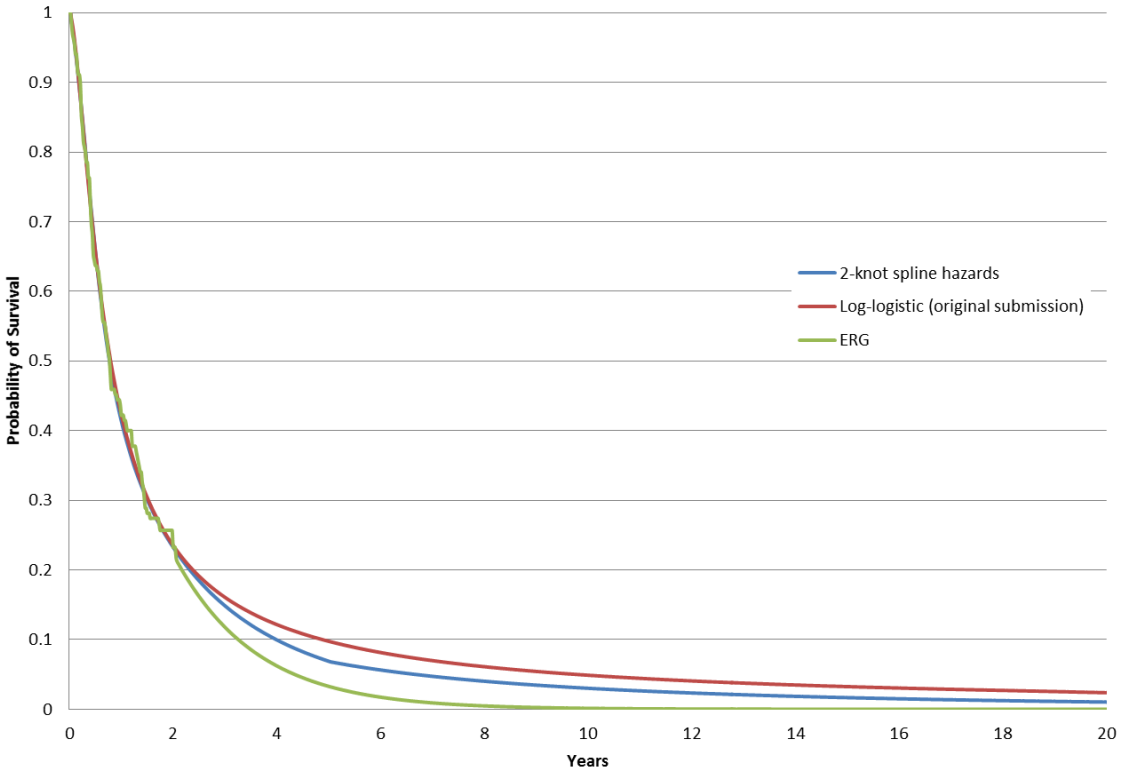
4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

Incorporation of user-friendly Opdivo® input cell to calculate results based on the simple confidential [redacted] discount ('nivolumab discount').

BMS have revised the economic model to reflect the assumptions that the Appraisal Committee considered most plausible; notably, the ERG's approaches to extrapolating progression-free survival. The modelling of treatment duration for nivolumab and docetaxel, and the amended drug costs,

alongside the BMS utility estimates. BMS considers that the overall survival extrapolation proposed by the evidence review group (fitting an exponential) is more conservative than the evidence suggests. We have therefore proposed an extrapolation model which is in between the BMS base case (log-logistic) and the ERG approach, which was presented as a scenario analysis in our original submission. Figure 1 compares the 2-knot spline hazards model with the previously proposed extrapolations and shows that it lies in between the two.

Figure 1. Overall survival extrapolations used in the BMS base case (log-logistic), ERG base case (exponential) and in this PAS submission (2-knot spline hazards).



The survival data using the 2-knot spline hazards model have been compared with clinical evidence from the CheckMate 003 study (described in our original submission), and this shows that the 2-knot spline hazards model is under-estimating OS in the 4-years for which data are available (Table 1).

Table 1: Validation of OS data using the 2-knot spline hazard model.

Data source	**Curve**	**Proportion alive**				
		6 months	1 year	2 years	3 years	4 years
CheckMate 003	Nivolumab OS	n/a	42.0%	24.0%	18.0%	15.0%
2-knot spline hazards	Nivolumab OS	66.5%	41.8%	23.4%	14.9%	10.0%

If, in line with the approach on TA 384 (nivolumab for treating advanced [unresectable or metastatic] melanoma), NICE review the evidence for nivolumab in squamous NSCLC in 2 years' time, CheckMate 017 4-year follow-up data will be available and based on the CheckMate 003 data presented above, we anticipate that the OS will be least as good as the 2 spline hazard OS extrapolation presented here and will not follow the ERG's conservative assumptions.

With these changes, in this revised analysis, BMS have considered the base case ICER for nivolumab compared with docetaxel to be [redacted] per QALY gained. BMS have applied the simple 'nivolumab discount', resulting in an ICER of £66,055. A scenario analysis demonstrating the cost-effectiveness of nivolumab if a 2-year clinical stopping rule is applied is presented (with justification of this provided below), in line with our original submission. Applying the simple 'nivolumab discount' to this model results in an ICER of £52,918.

Support for use of a clinical stopping rule

The patients enrolled in Phase III trials described in Checkmate 017 and 057 demonstrating the clinical efficacy and safety of nivolumab monotherapy in pre-treated advanced NSCLC patients who continued to receive study drug until their disease progressed, or they experienced unacceptable toxicity, as

per protocol (p177, section 5.8 of the CS). UK and international expert clinical opinion has confirmed that for those patients who have responded to nivolumab, treat to progression will not be reasonable in routine clinical practice, and that stopping therapy at an appropriate time point should be considered. Based on available data from BMS' Phase I study Checkmate 003 (CA209-003), looking at various doses of nivolumab across a range of tumour types, including pre-treated advanced NSCLC, UK clinicians agreed that limiting the maximum duration of treatment could be supported. Checkmate 003 had a protocol specified stopping rule for discontinuation of therapy at 96 weeks (1.8 years). The majority of patients (6/7) who achieved complete or partial response before 96 weeks, maintained their response. This treatment pattern is confirmed across all tumour types and all doses of nivolumab in Checkmate 003.

As mentioned in the company submissions, BMS are investigating the issue of a one year stopping rule in study Checkmate 153. Checkmate 153 is a phase IIIB/IV safety study which is more likely to represent real world clinical practice than CheckMate 017 and 057. In CheckMate 153, patients with stable disease at 1 year are randomised to stop treatment (with the option of retreatment on progression) vs. standard treatment to progression. The first data from the survival follow up of this study was expected to be available in Q2/3 2016. However fewer patients than expected have completed a year of treatment to be randomised into the two arms and a robust analysis cannot take place in Q2 2016 as stated at the second Appraisal Committee Meeting on 15th June 2016 and has been deferred to Q4 2016.

These data supports a 2 year duration of therapy for nivolumab monotherapy particularly for patients who have a complete or partial response at this time. This was acknowledged in the recent TA 384 (nivolumab for treating advanced [unresectable or metastatic] melanoma), in which the institute noted uncertainty of optimal duration of treatment, and commitment to re-review the evidence in two years when it may be more feasible to clarify optimal duration of treatment. Furthermore, another anti-PD1, pembroluzimab currently under NICE appraisal in NSCLC has suggested stopping anti-PD at 2 years

regardless of progression status, as discussed at the appraisal committee meeting on 29 June, suggesting that treatment to progression will not be the norm for these products in clinical practice.

We have therefore provided modelling for 2 years of treatment (see also Scenario 4 in the CS, described from page 177) to represent real world clinical practice until clarity can be provided.

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 PAS has been implemented in the model in the form of a simple discount, As such, the clinical effectiveness data are unchanged from those in the original BMS submission.

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'.

Not applicable

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.

Not applicable

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 1).

Table 1: Base-case cost-effectiveness results (with PAS)

	Nivolumab	Docetaxel
Intervention cost (£)	[redacted]	[redacted]
Treatment administration (£)	[redacted]	[redacted]
Treatment monitoring costs (£)	[redacted]	[redacted]
PF cost (£)	[redacted]	[redacted]
PD cost (£)	[redacted]	[redacted]
AE costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£; nivolumab – docetaxel)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference (nivolumab – docetaxel)	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference (nivolumab – docetaxel)	[redacted]	
ICER (£; nivolumab vs. docetaxel)	66,055	

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

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

Table 2: Base-case cost-effectiveness results (without PAS)

	Nivolumab	Docetaxel
Intervention cost (£)	[redacted]	[redacted]
Treatment administration costs (£)	[redacted]	[redacted]
Treatment monitoring costs (£)	[redacted]	[redacted]
PF cost (£)	[redacted]	[redacted]
PD cost (£)	[redacted]	[redacted]
AE costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£; nivolumab – docetaxel)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference (nivolumab – docetaxel)	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference (nivolumab – docetaxel)	[redacted]	
ICER (£; nivolumab vs. docetaxel)	[redacted]	

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

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 3.

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

Table 3: Base-case incremental results without the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5: Base-case incremental results with the PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66,055
Docetaxel	[redacted]	[redacted]	[redacted]				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

The base-case comparator in the model is docetaxel. Docetaxel is the current standard of care in pre-treated patients with squamous NSCLC in the UK and is the treatment likely to be displaced by the introduction of Nivolumab. The use of erlotinib in this patient cohort is limited and declining, and the economic case of docetaxel versus best supportive care has already been established (Holmes 2004) – therefore, erlotinib and BSC are not considered in this incremental analysis.

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.

Deterministic sensitivity analysis was undertaken by varying cost, utility and efficacy parameters by their confidence intervals or ±20% based on data availability. The results are presented in Table and in Figure below.

Table 6: Results of deterministic sensitivity analysis (with PAS)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis				
Discount rate - costs	Lower	[redacted]	[redacted]	70,521
	Higher	[redacted]	[redacted]	63,498
Discount rate - outcomes	Lower	[redacted]	[redacted]	57,553
	Higher	[redacted]	[redacted]	71,710
Average body weight	Lower	[redacted]	[redacted]	66,055
	Higher	[redacted]	[redacted]	66,055
BSA	Lower	[redacted]	[redacted]	66,055
	Higher	[redacted]	[redacted]	66,055
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	65,652
	Higher	[redacted]	[redacted]	66,458
Cost - PD state	Lower	[redacted]	[redacted]	64,213
	Higher	[redacted]	[redacted]	67,896
Terminal cost	Lower	[redacted]	[redacted]	66,095
	Higher	[redacted]	[redacted]	66,014
Administration cost – nivolumab	Lower	[redacted]	[redacted]	64,180
	Higher	[redacted]	[redacted]	67,930
Administration cost – docetaxel	Lower	[redacted]	[redacted]	66,283
	Higher	[redacted]	[redacted]	65,826
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	65,794
	Higher	[redacted]	[redacted]	66,762
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	66,202
	Higher	[redacted]	[redacted]	65,907
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	66,582
	Higher	[redacted]	[redacted]	65,568
Utility weight, PD	Lower	[redacted]	[redacted]	68,722
	Higher	[redacted]	[redacted]	63,587
Efficacy				
HR on OS - nivolumab	Lower	[redacted]	[redacted]	45,564
	Higher	[redacted]	[redacted]	81,352

BSA: Body Surface Area; CI: Confidence Interval; HR: Hazard Ratio; OS: Overall Survival; PD: Progressed Disease; PF: Progression-Free; PFS: Progression-Free Survival; QALY: Quality-Adjusted Life Year

Figure 2: Tornado diagram

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

Results of the probabilistic sensitivity analysis (PSA) on the PAS are shown in Table below. The PSA ICER is £57,047 per QALY gained. The PSA was run for 1000 iterations and the cost-effectiveness scatter plot and acceptability curve are shown in

Figure and
Figure , respectively.

Table 7: Probabilistic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab					57,047
Docetaxel					

ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years

Figure 3: Cost-effectiveness plane for nivolumab vs. docetaxel

Figure 4: Cost-effectiveness acceptability curve of nivolumab vs. docetaxel

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

In this analysis, the simple discount has been implemented alongside a 2-year clinical stopping rule, which is only applied to patients receiving nivolumab. The stopping rule is the maximum number of years that the patient can receive the drug, and therefore that the manufacturer can be reimbursed for per patient. Beyond the point at which the stopping rule is implemented (2 years), the patient will no longer receive the drug, and the manufacturer will not be reimbursed for the drug; that is, no drug acquisition costs are included in the model calculations.

Scenario 1: 2-year clinical stopping rule

Table 8: Scenario 1 - Summary of QALY gain by health state

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: Adverse Event; PD: Progressed Disease; PF: Progression-Free; QALY: Quality-Adjusted Life Year

*No utility is assigned to the death state

Table 9: Scenario 1 - Summary of costs

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: Adverse Event; PD: Progressed Disease; PF: Progression-Free

*Progressed disease includes the costs of managing patients who have progressed and end of life/terminal care. No costs are assigned to the death state.

Table 10: Scenario 1 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	£52,918
Docetaxel	[redacted]	[redacted]			

Abbreviations: QALY: Quality-Adjusted Life Year

Table 11: Results of deterministic sensitivity analysis (Scenario 1)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis				
Discount rate - costs	Lower	[redacted]	[redacted]	55,816
	Higher	[redacted]	[redacted]	51,326
Discount rate - outcomes	Lower	[redacted]	[redacted]	46,107
	Higher	[redacted]	[redacted]	57,449
Average body weight	Lower	[redacted]	[redacted]	52,918
	Higher	[redacted]	[redacted]	52,918
BSA	Lower	[redacted]	[redacted]	52,918
	Higher	[redacted]	[redacted]	52,918
Costs				

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Cost - PF state	Lower	[redacted]	[redacted]	52,514
	Higher	[redacted]	[redacted]	53,321
Cost - PD state	Lower	[redacted]	[redacted]	51,076
	Higher	[redacted]	[redacted]	54,759
Terminal cost	Lower	[redacted]	[redacted]	52,958
	Higher	[redacted]	[redacted]	52,877
Administration cost – nivolumab	Lower	[redacted]	[redacted]	51,464
	Higher	[redacted]	[redacted]	54,371
Administration cost – docetaxel	Lower	[redacted]	[redacted]	53,146
	Higher	[redacted]	[redacted]	52,689
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	52,680
	Higher	[redacted]	[redacted]	53,563
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	53,065
	Higher	[redacted]	[redacted]	52,770
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	53,340
	Higher	[redacted]	[redacted]	52,528
Utility weight, PD	Lower	[redacted]	[redacted]	55,054
	Higher	[redacted]	[redacted]	50,941
Efficacy				
HR on OS - nivolumab	Lower	[redacted]	[redacted]	37,873
	Higher	[redacted]	[redacted]	64,149

BSA: Body Surface Area; CI: Confidence Interval; HR: Hazard Ratio; OS: Overall Survival; PD: Progressed Disease; PF: Progression-Free; PFS: Progression-Free Survival; QALY: Quality-Adjusted Life Year

Figure 5: Tornado Diagram (Scenario 1)

[redacted]

Table 12: Probabilistic results (Scenario 1)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	46,496
Docetaxel	[redacted]	[redacted]			

ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years

Figure 3: Cost-effectiveness plane for nivolumab vs. docetaxel (Scenario 1)

[redacted]

Figure 4: Cost-effectiveness acceptability curve of nivolumab vs. docetaxel (Scenario 1)

[redacted]

[redacted]

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.

The PAS is not dependent on any clinically variable parameters.

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.

Table 4: Results showing the impact of patient access scheme on ICERs for scenarios

ICERs	**Nivolumab vs. docetaxel**	
	Without PAS	With PAS
Base-case	[redacted]	£66,055
Scenario 1: two-year stopping rule	[redacted]	£52,918

PAS: patient access scheme.

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.

PAS agreement form (including terms and conditions): This is the BMS Standard Terms and Conditions which will be used for supplying Opdivo®

5.2 Appendix B: Details of outcome-based schemes

Not applicable

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.