NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900]

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) –** released October 2016

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Bristol-Myers Squibb Pharmaceuticals
   - British Thoracic Society
   - Roy Castle Lung Cancer Foundation
   - National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists, British Thoracic Oncology Group – joint response
   - Royal College of Pathologists

   'No comment' response received from the Department of Health

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

4. **Public petitions received in response to the Appraisal Consultation Document**

February 2017

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

6. **Decision Support Unit (DSU) specification**

7. **Decision Support Unit (DSU) Report**

8. **Company response & new evidence in response to the Decision Support Unit Report** prepared by Bristol-Myers Squibb Pharmaceuticals

August 2017

9. **Company new analyses** prepared by Bristol-Myers Squibb Pharmaceuticals

10. **Company response to questions from NICE (1)** prepared by Bristol-Myers Squibb Pharmaceuticals

11. **Company response to questions from NICE (2)** prepared by Bristol-Myers

Squibb Pharmaceuticals

12. Decision Support Unit (DSU) critique of new analyses

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 non-squamous non-small-cell lung cancer

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD2)

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 (BMS)	<u>PD-L1 restriction</u> BMS believes that it is inappropriate to focus on a PD-L1 sub-grouping and that NICE has exceeded its powers by seeking to define a subgroup in this manner for consideration for the CDF. BMS are also unclear if this approach is a suitable basis for providing guidance to the NHS. The committee noted that the marketing authorisation for nivolumab does not restrict nivolumab therapy according to a defined PD-L1 expression level, nor was it required by the scope for the appraisal. It is therefore a surprise to us that the recommendation from NICE states a restriction based on a 10% PD-L1 expression level. BMS feels this recommendation is unreasonable and perverse and that it fails to take into consideration the plethora of evidence presented throughout the appraisals in support of treating a wider patient population. The registration study for the non-squamous population (CheckMate-057) was powered to show superiority over docetaxel in patients with relapsed advanced metastatic NSCLC, regardless of PD-L1 status. The primary end point of superior overall survival (OS) was met with a 2.8-month difference in median OS (HR 0.75, 95% CI 0.63, 0.91), a 12% absolute difference in the survival rate at 1 year (51% vs 39%), demonstrating a clearly positive statistically significant and clinically meaningful benefit regardless of PD-L1 expression. Similarly, the registration study for the squamous population (CheckMate-017) was also powered to show superiority over docetaxel in patients with relapsed advanced metastatic NSCLC regardless of PD-L1 status; the median OS showed a 2.3-month difference (HR 0.62, 95% CI 0.47, 0.80) and 1 year OS rate of 42% (vs 24%).	Comment noted. The committee acknowledged the response from the company and other consultees and considered new evidence and analyses for the whole population. The committee also considered the further new evidence that was submitted by BMS and reviewed by the Decision Support Unit (DSU) before the fifth committee meeting. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base.

Consultee	Comment [sic]	Response
	The EMA assessed the risk benefit profile of nivolumab to be favourable in all patients, regardless of PD-L1 status. Testing was not therefore required by the EMA to select patients for eligibility to treatment. During the process of marketing authorisation approval, post hoc analyses were requested by the CHMP. The SmPC therefore includes additional PD-L1 analyses at different intervals and at the 50% threshold level for ORR and OS in Section 5.1 and also warning statement for early deaths in Section 4.4. However, these post-hoc analysis results should be interpreted with caution for several reasons: - the analysis was retrospective, the subgroup sample sizes are small, and the PD-L1 test was not analytically validated at the 10% or 50% expression levels at the time of the analysis. The information requested by the CHMP has been provided in the SmPC for information but the licence remains for all patients regardless of PD-L1 expression level. PD-L1 is an imperfect predictive biomarker. Testing methodologies are still being developed and there is no single standardised test routinely used by the NHS. The tests have a high positive predictive value but a low negative predictive value i.e. if the patient is positive they are more likely to have a good response, but if they are negative they may still respond to nivolumab and may even achieve complete response. Not only has it been demonstrated that patients benefit from nivolumab regardless of PD-L1 expression, there are also numerous limitations to using PD-L1 expression as a biomarker, and these include the following points: • Heterogeneity of PD-L1 expression throughout the tumour therefore a biopsy may not be representative of PD-L1 expression within the whole tumour. • Unlike tumour driver mutations such as EGFR, protein expression such as that of PD-L1 may vary over time and after prior treatments including chemotherapy. A biopsy at diagnosis may therefore not be representative of PD-L1 expression level at the time of relapse and treatment decision making.	

Consultee	Comment [sic]	Response
	• The level of expression is a continuous variable, and the appropriate threshold for positivity is debated. BMS is not defining a "cut-off" for PD-L1 expression level, as we do not consider there is a "cut-off" below which patients should not be considered for treatment with nivolumab in the relapsed advanced metastatic setting. Observed clinical activity in PD-L1 low or non-expressors, suggests that application of stringent PD-L1 cut-offs would likely result in exclusion of patients who would derive benefit from nivolumab treatment. • The research community are currently discussing that a more complex, multicomponent predictive biomarker system will be required to refine appropriate patient selection for PD-1 blockade and what that should be. As well as scientific arguments against a PD-L1 restriction, there is also a lack of consistency at NICE. In the previous ACD for squamous NSCLC (issued 15th Dec 2015), it states in Section 4.5 that the PD-L1 subgroup analyses in CheckMate-017 provided no evidence of a significantly different effect in any of the subgroups assessed, including the proposed biomarker: PD-L1. The Committee highlighted that PD-L1 expression status is dynamic and can change over time; it therefore considered that these results should be viewed with caution. The Committee concluded that it was not possible to identify any subgroups for whom nivolumab would provide particular benefits, and so it was unable to make recommendations for nivolumab in specific subgroups. Having drawn this conclusion it is difficult to see how NICE can now issue a new document which suggests that the efficacy of nivolumab should be restricted to a PD-L1 sub-group.	

BMS	Optimal duration of treatment There is uncertainty as to the optimal duration of therapy for nivolumab. The mechanism of action of nivolumab is that it switches on the immune system 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 in responders this activity may remain after the administration of the drug is withdrawn. The patients enrolled in both Checkmate 017 and 057 continued to receive study drug until their disease progressed, or they experienced unacceptable toxicity, as per the protocol. UK and international expert clinical opinion is that for those patients who have responded to nivolumab including for other indications and anti-PD1/L1 agents, treat to progression is likely to become redundant in clinical practice in future, 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, which 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 complete or partial response or stable disease at 1 year are randomised to stop treatment (with the option of retreatment on progression) vs. standard treatment to progression. These data support a 2 year duration of therapy for nivolumab monotherapy, particularly for patients who have a complete or partial response at this time as a conservative stopping point for therapy. This was acknowledged in the recent TA 384 (nivolumab for treating advanced [unresectable or metastatic] melanoma). There the Institute noted uncertainty around the optimal duration of treatment, and made a commitment to re-review the evidence	Comment noted. The committee examined the additional evidence submitted by the company and comments from consultees. It took all the available evidence into consideration when reaching its conclusion on the proposed stopping rule (FAD, section 4.21).

Consultee	Comment [sic]	Response
	after 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 data supporting stopping treatment at 2 years regardless of progression status, as discussed at the appraisal committee meeting on 29th June and again on 26th October. This suggests that treatment to progression will not be the norm for these products in clinical practice. This view was also expressed in the comments from NHSE received as part of that ongoing appraisal. We have therefore provided the results for the modelling when 1 and 2 years of treatment are assumed to represent real world clinical practice, until definitive clarity can be provided.	
BMS	Comparators Pembrolizumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have at least 1 chemotherapy regimen. Within this license, both squamous and non-squamous histologies of NSCLC are included. Nivolumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. For consistency and given that both treatment options relate to similar patient populations, the comparators in both appraisals should be the same. In fact, nintedanib plus docetaxel is included in one appraisal but not the other. BMS has raised this during the consultation opportunities for the pembrolizumab appraisal requesting that the comparators be consistent. This point was discussed at the recent appraisal committee meeting for Pembrolizumab on October 26th, and the committee decided that nintedanib plus docetaxel should not be a comparator in that appraisal. BMS therefore requests that nintedanib should be removed from the comparators for the non-squamous nivolumab appraisal.	Comment noted, The committee has considered all comparators identified in the final NICE scope and made judgements on their appropriateness (in line with NICE Methods Guide Section 6.2). Please see the FAD, section 4.3, for committee's conclusions on comparator technologies.

Consultee	Comment [sic]	Response
BMS	Concluding remarks Nivolumab is an innovative treatment option which was EAMS designated and offers a survival and HRQoL benefit for all patients, regardless of PD-L1 expression. It is also associated with less frequent adverse events and related treatment discontinuation compared to docetaxel chemotherapy. The MHRA awarded nivolumab a PIM designation in the treatment of locally advanced or metastatic NSCLC. This represents a long-awaited and remarkable advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. BMS therefore requests NICE to remove from the recommendation the limitation to treatment only where there is PD-L1 expression in Sections 1.1 and 1.2 of the second ACDs. In addition, BMS urges NICE to work with BMS to find a mutually workable solution to make nivolumab available to all eligible patients in England and Wales.	Comments noted. The committee has considered the innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured by the QALY measure (in line with NICE Methods Guide Section 6.3.3). Please see the FAD, section 4.27, for committee's conclusions on innovation.
British Thoracic Society	The Society supports the recommendation that the committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund.	Comments noted. The committee noted that at the fifth meeting the company presented new evidence and a commercial access agreement proposal for inclusion in the CDF. It considered the new evidence and made its recommendation in respect of the whole population. Please see section 4.28-4.35 for committee's conclusion on the CDF.

Consultee	Comment [sic]	Response
National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists, British Thoracic Oncology Group (NCRI, ACP, RCP, RCR, BTOG)	The NCRI-ACP-RCP-RCR-BTOG are grateful for the opportunity to respond to the above consultation. We are disappointed that the committee has not approved nivolumab in this TA. We wish to raise the following points: PDL1 expression The CM057 trial demonstrated the superior overall survival for nivolumab over docetaxel. Whilst efficacy changed by PDL1 expression status the nature of PDL1 expression is variable, both within tumours and with time. Hence, we feel that the decision to implement a 10% threshold is arbitrary to fit the modelled survival benefit lacking scientific rational. We note that patients with PDL1 < 10% derived a survival benefit from nivolumab over docetaxel with far less toxicity, including that associated with inpatient admission.	Comment noted. The committee acknowledged the response from the company and other consultees and considered new evidence and analyses submitted by BMS and reviewed by the DSU. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base.
NCRI, ACP, RCP, RCR, BTOG	GSCF use The toxicities of docetaxel (specifically febrile neutropenia) are likely to be underestimated in CM057 compared to English practice, since in CM057 GCSF prophylaxis was allowed for docetaxel. The use of GCSF prophylaxis is not approved for use by NICE (CG151), hence not widely used which drives a more conservative dosing approach and a greater likelihood of discontinuation potentially leading to poorer docetaxel outcomes than those in observed in CM057. Therefore, the use of nivolumab in this setting is desirable for toxicity/efficacy reasons even in patients with <10% PDL1 expression.	Comment noted. The committee acknowledged that docetaxel is associated with high levels of toxicity and that people would welcome additional treatment options for non-squamous NSCLC. Please also see FAD, Section 4.1.
NCRI, ACP, RCP, RCR, BTOG	PDL1 expression variability PDL1 expression is known to be heterogeneous. Expression is known to heterogenous within tumours and also changes over time and after therapies (eg radiotherapy/chemotherapy). Perversely, limiting nivolumab by expression level will drive patients to re-biopsy to achieve a > 10% PDL1 positive status following chemo- and radiotherapy. This will increase overall NHS costs and put patients through unnecessary morbidity (with small risk of mortality).	The committee acknowledged the response from the company and other consultees and considered new evidence and analyses submitted by BMS and reviewed by the DSU. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base.

Consultee	Comment [sic]	Response
NCRI, ACP, RCP, RCR, BTOG	CDF data collection We have major concerns the logistics of implementing prospective data capture in the CDF and would question if sufficient resource has been allocated for the program to achieve satisfactory data capture and analysis. This will be challenging and if under resourced the data capture element will place a large administrative burden on individual consultant oncologists, resulting in incomplete collection, poor data accuracy and hence outcomes would not be representative. It is also not clear that additional data will reduce uncertainty on clinical effectiveness in patients with at least 10% PDL1 expression. Such a data capture exercise will likely need a randomized comparator (docetaxel-nintednib) and it would be perverse to randomize patients away from nivolumab which is licensed for this indication. Moreover, the outcomes would not be directly comparable to CM057 given the change in comparator from docetaxel (CM057) to docetaxel-nintedanib.	Comments noted. The committee noted that at the fifth meeting the company presented new evidence and a commercial access agreement proposal for inclusion in the CDF. It considered the new evidence and made its recommendation in respect of the whole population. Please see section 4.28-4.35 for committee's conclusion on the CDF.
NCRI, ACP, RCP, RCR, BTOG	Stopping rule The optimal duration of dosing of nivolumab remains unknown and a focus for future research. Given the findings currently of the CM003 long term survival data which implemented a 96-week stopping rule, clinicians would be satisfied to discontinue at two years on the basis of current data. We see no reason why such a rule could not be implemented in routine practice.	Comment noted. The committee examined the additional evidence submitted by the company and comments from consultees. It took these into consideration when reaching its conclusion on the proposed stopping rule (FAD, section 4.21).
NCRI, ACP, RCP, RCR, BTOG	National inconsistency We note that the SMC have approved nivolumab for use in this indication without PDL1 criteria and limited to two years. An inconsistent national approach for this indication will significantly prejudice survival outcomes against NHS England patients.	Comment noted. The committee has to appraise the clinical and cost effectiveness evidence of the technology and can only provide guidance to the NHS in England. The recommendation made is based upon the clinical and cost effectiveness evidence and can be found in section 4 of the FAD.

Consultee	Comment [sic]	Response
Royal College of Pathologists	My only comment is that, if there is a recommendation for use of nivolumab at a level of >10% staining, then the impact on laboratory resources (pathologist and biomedical scientists) will need to be taken into account as immunohistochemistry will be necessary on any non-small cell carcinoma being considered for therapy.	Comment noted. The committee acknowledged the response from the company and other consultees and considered new evidence and analyses submitted by BMS and reviewed by the DSU. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base..
Roy Castle Lung Cancer Foundation	We are very disappointed that the second Appraisal Committee decision is not to recommend Nivolumab in this indication.	Comment noted. The committee noted that at the fifth meeting the company presented new evidence and a commercial access agreement proposal for inclusion in the CDF. It considered the new evidence and made its recommendation in respect of the full evidence base. Please see section 4.27-4.35 for committee's conclusion on the CDF.
RCLCF	In our opinion, immunotherapy represents a major new development in the treatment of non small cell lung cancer (nsclc) patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. It is therefore important that a PD-L1 inhibitor be available in the algorithm of lung cancer care in England. Ideally, we would wish to see this achieved through routine commissioning, to ensure equity of access. However, in reducing uncertainty on issues of effectiveness, we would welcome a period of availability of access through the Cancer Drugs Fund.	Comment noted. The committee acknowledged the response from the company and other consultees and considered new evidence and analyses submitted by BMS and reviewed by the DSU. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base.

Consultee	Comment [sic]	Response
RCLCF	We note the Appraisal Committee's comments (section 4.8), that those patients with a PD-L1 expression of at least 10%, seem to have the most potential to benefit from this treatment. Whilst we acknowledge that PD-L1 expression is an important mechanism of action, we have not seen, nor are we able to comment on, any rationale or research evidence for a 'cut off' at this 10% level. We would encourage dialogue with clinical experts on this point. We further note the Appraisal Committee's invitation to the manufacturer to submit a proposal for inclusion in the Cancer Drugs Fund, detailing, for this 'at least 10% PD-L1 expression' subgroup, how uncertainties may be resolved over the CDF period. We welcome, through this invitation, the ongoing dialogue on availability of this therapy and hope this will have a constructive outcome.	Comment noted. The committee noted that at the fifth meeting the company presented new evidence and a commercial access agreement proposal for inclusion in the CDF. It considered the new evidence and made its recommendation in respect of the whole population (FAD, section 1.1). Please see section 4.28-4.35 for committee's conclusion on the CDF. .
RCLCF	We note that the Appraisal Committee has reached this negative decision, based on cost issues. **On behalf of the many lung cancer patients who would derive benefit from this innovative therapy, we strongly urge constructive dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues and issues of uncertainty are addressed.** Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement 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.	Comment noted. The committee acknowledged that docetaxel is associated with high levels of toxicity and that people would welcome additional treatment options for non-squamous NSCLC. Please also see FAD section 4.1.

Summary of comments received from members of the public

Theme	Response
Nivolumab should be made available to all patients. The evidence base shows that it extends life and improves quality of life.	The committee agree that an additional treatment option for non-squamous NSCLC is welcomed, but notes that the recommendation has to be made based upon the clinical and cost effectiveness evidence.

Nivolumab has been recommended in Scotland and therefore it should be made available in England and Wales as well.	The committee has to appraise the clinical and cost effectiveness evidence of the technology and can only provide guidance to the NHS in England.
Nivolumab has been approved in the US, Japan and other countries around the world.	The committee has to appraise the clinical and cost effectiveness evidence of the technology and can only provide guidance to the NHS in England.
Nivolumab give patients and their families hope. Denying people the chance to live is unethical and deprived their human rights.	The committee agree that an additional treatment option for non-squamous NSCLC is welcomed, but notes that the recommendation has to be made based upon the clinical and cost effectiveness evidence
Lung medications should be made available just like medications for heart diseases.	The committee has to appraise the clinical and cost effectiveness evidence of the technology in its licensed indication. Recommendations are made based on the appraisal of this evidence for referred every indication.
Nivolumab should be made available provisionally and then if evidence shows that it is not effective, the guidance should be reviewed.	The committee invited the company to submit an application for the Cancer Drugs Fund in a subgroup of the population. The committee noted that at the fifth meeting the company presented new evidence and a commercial access agreement proposal for inclusion in the CDF The committee based its decision on the full clinical and cost effectiveness evidence. Please see FAD, section 4.
A petition has been submitted to NICE and NICE has declined to discuss the petition with the organisers. NICE should be willing to discuss their recommendations, this is not fulfilled by the publication of the Appraisal consultation document, where the information is very technical.	The petition was received by the appraisal committee and considered in the committee meeting alongside other consultee and commentator responses. Please see FAD, section 4.10.
The description of the evidence in the ACD focuses on the evidence that comes from the company and doesn't seem to take into consideration the patients views.	The committee received and considered written submissions from patient groups and experts. In addition, the committee heard from patient experts during the committee meeting. These helped the committee understand the patients' perspective. Please also see FAD, section 3 for full list of the evidence and section 4.1 on the statements from patient experts at the meeting.
Nivolumab should be made available via the CDF on a provisional basis.	The committee noted that the company did not submit a proposal for inclusion in the CDF and considered new evidence in respect of the

	whole population. Please see section 4.28–4.35 for committee's conclusion on the CDF.
The decision should not be made only based on costs.	The committee has to appraise the clinical and cost effectiveness evidence of the technology.
Spending money and time on cancer research and then not approving a drug does not make sense.	The committee has to appraise the technology and base its decision on the clinical and cost effectiveness evidence of the technology.
NICE and the company should engage in negotiations about lowering the price for this drug, to make it available for patients.	NICE cannot negotiate price and must appraise the drug at the price it is/would be available to the NHS.
Even little extension to life is valued highly by patients and relatives.	The committee agree that an additional treatment option for non-squamous NSCLC is welcomed. Please also see FAD section 4.1.
Of the 9.6 million smokers in the UK, there are different rates of smoking among men and women. Action on Smoking and Health (ASH) reported in October 2016 that 20% of men smoke, whereas only 17% of women smoke in the UK. Hence there are aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination on the grounds of gender.	The impact on equality has been assessed during this appraisal according to the principles of the NICE equality scheme and recorded in the *Equality impact assessment* (available in the committee papers online).
The clinical trial evidence does not support that nivolumab should be recommended for people only with PD-L1 expression ≥ 10%. In the clinical trial ChekMate-057 there was a trend to improved effectiveness with increasing PD-L1 expression, but there was no defined threshold. An attempt to define a threshold on retrospective modelling of subgroup analyses of cohorts (when there are small numbers in each group) is not valid and would not be acceptable if used in support of a funding application or in devising clinical guidelines. We also believe the committee has not fully considered how this decision could be implemented in the NHS. Many patients with thoracic malignancies will not have suitable samples for PDL1 analysis, thus repeat biopsy may be required. That will place our patients at risks of additional procedures and will also put additional strain on respiratory diagnostic services which are already struggling with meeting government targets as to speed of diagnosis and appropriate treatment. We also do not think that most UK pathology departments are set-up to deliver this. This test requires interpretation	The committee acknowledged the response from the company and other consultees and considered new evidence and analyses for the whole population. The committee also considered the further new evidence that was submitted by BMS and reviewed by the Decision Support Unit (DSU) before the fifth committee meeting. The recommendation made in the Final Appraisal Determination (FAD, Section1.1) is made in respect of the full evidence base.

by skilled respiratory pathologists employing assays on a validated platform. It is clear that this is not deliverable with the present set-up; this will in particular disadvantage patients diagnosed and treated at some of the smaller cancer units.	

Bristol-Myers Squibb Pharmaceuticals Limited

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National Institute for Health and Care Excellence
10 Spring Gardens
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SW1A 2BU

4th November 2016

Dear Sir / Madam,

Re: ACD - Nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer [ID900]

Thank you for the opportunity to respond to this ACD.

Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd disagree with the proposed recommendation for nivolumab for previously treated locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) in the second Appraisal Consultation Document (ACD) issued by NICE on the 14th October 2016.

Our rationale is explained below in detail but our major concern is the proposed restriction to adults with a PD-L1 expression of less than 10%.

BMS is keen to continue working with NICE to find a mutually agreeable way forward that will allow nivolumab to be used in the patient group envisaged by the license in both England and Wales.

Yours Sincerely,

[redacted]

PD-L1 restriction

BMS believes that it is inappropriate to focus on a PD-L1 sub-grouping and that NICE has exceeded its powers by seeking to define a subgroup in this manner for consideration for the CDF. BMS are also unclear if this approach is a suitable basis for providing guidance to the NHS.

The committee noted that the marketing authorisation for nivolumab does not restrict nivolumab therapy according to a defined PD-L1 expression level, nor was it required by the scope for the appraisal. It is therefore a surprise to us that the recommendation from NICE states a restriction based on a 10% PD-L1 expression level. BMS feels this recommendation is unreasonable and perverse and that it fails to take into consideration the plethora of evidence presented throughout the appraisals in support of treating a wider patient population.

The registration study for the non-squamous population (CheckMate-057) was powered to show superiority over docetaxel in patients with relapsed advanced metastatic NSCLC, regardless of PD-L1 status. The primary end point of superior overall survival (OS) was met with a 2.8-month difference in median OS (HR 0.75, 95% CI 0.63, 0.91), a 12% absolute difference in the survival rate at 1 year (51% vs 39%), demonstrating a clearly positive statistically significant and clinically meaningful benefit regardless of PD-L1 expression. Similarly, the registration study for the squamous population (CheckMate-017) was also powered to show superiority over docetaxel in patients with relapsed advanced metastatic NSCLC regardless of PD-L1 status; the median OS showed a 2.3-month difference (HR 0.62, 95% CI 0.47, 0.80) and 1 year OS rate of 42% (vs 24%).

The EMA assessed the risk benefit profile of nivolumab to be favourable in all patients, regardless of PD-L1 status. Testing was not therefore required by the EMA to select patients for eligibility to treatment.

During the process of marketing authorisation approval, post hoc analyses were requested by the CHMP. The SmPC therefore includes additional PD-L1 analyses at different intervals and at the 50% threshold level for ORR and OS in Section 5.1 and also warning statement for early deaths in Section 4.4.

However, these post-hoc analysis results should be interpreted with caution for several reasons:
- the analysis was retrospective, the subgroup sample sizes are small, and the PD-L1 test was not analytically validated at the 10% or 50% expression levels at the time of the analysis.

The information requested by the CHMP has been provided in the SmPC for information but the licence remains for all patients regardless of PD-L1 expression level.

PD-L1 is an imperfect predictive biomarker. Testing methodologies are still being developed and there is no single standardised test routinely used by the NHS. The tests have a high positive predictive value but a low negative predictive value i.e. if the patient is positive they are more

likely to have a good response, but if they are negative they may still respond to nivolumab and may even achieve complete response.

Not only has it been demonstrated that patients benefit from nivolumab regardless of PD-L1 expression, there are also numerous limitations to using PD-L1 expression as a biomarker, and these include the following points:

- Heterogeneity of PD-L1 expression throughout the tumour therefore a biopsy may not be representative of PD-L1 expression within the whole tumour.
- Unlike tumour driver mutations such as EGFR, protein expression such as that of PD-L1 may vary over time and after prior treatments including chemotherapy. A biopsy at diagnosis may therefore not be representative of PD-L1 expression level at the time of relapse and treatment decision making.
- The level of expression is a continuous variable, and the appropriate threshold for positivity is debated. BMS is not defining a "cut-off" for PD-L1 expression level, as we do not consider there is a "cut-off" below which patients should not be considered for treatment with nivolumab in the relapsed advanced metastatic setting. Observed clinical activity in PD-L1 low or non-expressors, suggests that application of stringent PD-L1 cut-offs would likely result in exclusion of patients who would derive benefit from nivolumab treatment.
- The research community are currently discussing that a more complex, multicomponent predictive biomarker system will be required to refine appropriate patient selection for PD-1 blockade and what that should be.

As well as scientific arguments against a PD-L1 restriction, there is also a lack of consistency at NICE. In the previous ACD for squamous NSCLC (issued 15th Dec 2015), it states in Section 4.5 that the PD-L1 subgroup analyses in CheckMate-017 provided no evidence of a significantly different effect in any of the subgroups assessed, including the proposed biomarker: PD-L1. The Committee highlighted that PD-L1 expression status is dynamic and can change over time; it therefore considered that these results should be viewed with caution. The Committee concluded that it was not possible to identify any subgroups for whom nivolumab would provide particular benefits, and so it was unable to make recommendations for nivolumab in specific subgroups.

Having drawn this conclusion it is difficult to see how NICE can now issue a new document which suggests that the efficacy of nivolumab should be restricted to a PD-L1 sub-group.

Optimal duration of treatment

There is uncertainty as to the optimal duration of therapy for nivolumab. The mechanism of action of nivolumab is that it switches on the immune system 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 in responders this activity may remain after the administration of the drug is withdrawn.

The patients enrolled in both Checkmate 017 and 057 continued to receive study drug until their disease progressed, or they experienced unacceptable toxicity, as per the protocol. UK and international expert clinical opinion is that for those patients who have responded to nivolumab including for other indications and anti-PD1/L1 agents, treat to progression is likely to become redundant in clinical practice in future, 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, which 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 complete or partial response or stable disease at 1 year are randomised to stop treatment (with the option of retreatment on progression) vs. standard treatment to progression.

These data support a 2 year duration of therapy for nivolumab monotherapy, particularly for patients who have a complete or partial response at this time as a conservative stopping point for therapy. This was acknowledged in the recent TA 384 (nivolumab for treating advanced [unresectable or metastatic] melanoma). There the Institute noted uncertainty around the optimal duration of treatment, and made a commitment to re-review the evidence after 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 data supporting stopping treatment at 2 years regardless of progression status, as discussed at the appraisal committee meeting on 29th June and again on 26th October. This suggests that treatment to progression will not be the norm for these products in clinical practice. This view was also expressed in the comments from NHSE received as part of that ongoing appraisal.

We have therefore provided the results for the modelling when 1 and 2 years of treatment are assumed to represent real world clinical practice, until definitive clarity can be provided.

Comparators

Pembrolizumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have at least

1 chemotherapy regimen. Within this license, both squamous and non-squamous histologies of NSCLC are included.

Nivolumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

For consistency and given that both treatment options relate to similar patient populations, the comparators in both appraisals should be the same. In fact, nintedanib plus docetaxel is included in one appraisal but not the other. BMS has raised this during the consultation opportunities for the pembrolizumab appraisal requesting that the comparators be consistent. This point was discussed at the recent appraisal committee meeting for Pembrolizumab on October 26th, and the committee decided that nintedanib plus docetaxel should not be a comparator in that appraisal. BMS therefore requests that nintedanib should be removed from the comparators for the non-squamous nivolumab appraisal.

Concluding remarks

Nivolumab is an innovative treatment option which was EAMS designated and offers a survival and HRQoL benefit for all patients, regardless of PD-L1 expression. It is also associated with less frequent adverse events and related treatment discontinuation compared to docetaxel chemotherapy. The MHRA awarded nivolumab a PIM designation in the treatment of locally advanced or metastatic NSCLC. This represents a long-awaited and remarkable advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. BMS therefore requests NICE to remove from the recommendation the limitation to treatment only where there is PD-L1 expression in Sections 1.1 and 1.2 of the second ACDs. In addition, BMS urges NICE to work with BMS to find a mutually workable solution to make nivolumab available to all eligible patients in England and Wales.

British Thoracic Society

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To be submitted via NICE docs

26 October 2016

Dear Sir,

ACD2 - Consultees & Commentators: Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [900]

Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD).

The Society supports the recommendation that the committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund.

Yours faithfully,

[redacted]
[redacted]
British Thoracic Society

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD2) on Nivolumab for previously treated, locally advanced or metastatic non squamous non small cell lung cancer. [ID900]

This response is submitted by Roy Castle Lung Cancer Foundation.

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

- In our opinion, immunotherapy represents a major new development in the treatment of non small cell lung cancer (nsclc) patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. It is therefore important that a PD-L1 inhibitor be available in the algorithm of lung cancer care in England. Ideally, we would wish to see this achieved through routine commissioning, to ensure equity of access. However, in reducing uncertainty on issues of effectiveness, we would welcome a period of availability of access through the Cancer Drugs Fund.

- We note the Appraisal Committee's comments (section 4.8), that those patients with a PD-L1 expression of at least 10%, seem to have the most potential to benefit from this treatment. Whilst we acknowledge that PD-L1 expression is an important mechanism of action, we have not seen, nor are we able to comment on, any rationale or research evidence for a 'cut off' at this 10% level. We would encourage dialogue with clinical experts on this point.

  We further note the Appraisal Committee's invitation to the manufacturer to submit a proposal for inclusion in the Cancer Drugs Fund, detailing, for this 'at least 10% PD-L1 expression' subgroup, how uncertainties may be resolved over the CDF period. We welcome, through this invitation, the ongoing dialogue on availability of this therapy and hope this will have a constructive outcome.

- We note that the Appraisal Committee has reached this negative decision, based on cost issues. **On behalf of the many lung cancer patients who would derive benefit from this innovative therapy, we strongly urge constructive dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues and issues of uncertainty are addressed**. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement 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
November 2016

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From [redacted]

24 October 2016

Dear Sir or Madam

Re: Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR-BTOG are grateful for the opportunity to respond to the above consultation. We are disappointed that the committee has not approved nivolumab in this TA. We wish to raise the following points:

PDL1 expression

The CM057 trial demonstrated the superior overall survival for nivolumab over docetaxel. Whilst efficacy changed by PDL1 expression status the nature of PDL1 expression is variable, both within tumours and with time. Hence, we feel that the decision to implement a 10% threshold is arbitrary to fit the modelled survival benefit lacking scientific rational. We note that patients with PDL1 < 10% derived a survival benefit from nivolumab over docetaxel with far less toxicity, including that associated with inpatient admission.

GSCF use

The toxicities of docetaxel (specifically febrile neutropenia) are likely to be underestimated in CM057 compared to English practice, since in CM057 GCSF prophylaxis was allowed for docetaxel. The use of GCSF prophylaxis is not approved for use by NICE (CG151), hence not widely used which drives a more conservative dosing approach and a greater likelihood of discontinuation potentially leading to poorer docetaxel outcomes than those in observed in CM057. Therefore, the use of nivolumab in this setting is desirable for toxicity/efficacy reasons even in patients with <10% PDL1 expression.

PDL1 expression variability

PDL1 expression is known to be heterogeneous. Expression is known to heterogenous within tumours and also changes over time and after therapies (eg radiotherapy/chemotherapy). Perversely, limiting nivolumab by expression level will drive patients to re-biopsy to achieve a > 10% PDL1 positive status following chemo- and radiotherapy. This will increase overall NHS costs and put patients through unnecessary morbidity (with small risk of mortality).

CDF data collection

We have major concerns the logistics of implementing prospective data capture in the CDF and would question if sufficient resource has been allocated for the program to achieve satisfactory data capture and analysis. This will be challenging and if under resourced the data capture element will place a large administrative burden on individual consultant oncologists, resulting in incomplete collection, poor data accuracy and hence outcomes would not be representative. It is also not clear that additional data will reduce uncertainty on clinical effectiveness in patients with at least 10% PDL1 expression. Such a data capture exercise will likely need a randomized comparator (docetaxel-nintednib) and it would be perverse to randomize patients away from nivolumab which is licensed for this indication. Moreover, the outcomes would not be directly comparable to CM057 given the change in comparator from docetaxel (CM057) to docetaxel-nintedanib.

Stopping rule

The optimal duration of dosing of nivolumab remains unknown and a focus for future research. Given the findings currently of the CM003 long term survival data which implemented a 96-week stopping rule, clinicians would be satisfied to discontinue at two years on the basis of current data. We see no reason why such a rule could not be implemented in routine practice.

National inconsistency

We note that the SMC have approved nivolumab for use in this indication without PDL1 criteria and limited to two years. An inconsistent national approach for this indication will significantly prejudice survival outcomes against NHS England patients.

Yours faithfully

[redacted]

I apologise that this is late and may not be included – there are just too many emails.

My only comment is that, if there is a recommendation for use of nivolumab at a level of >10% staining, then the impact on laboratory resources (pathologist and biomedical scientists) will need to be taken into account as immunohistochemistry will be necessary on any non-small cell carcinoma being considered for therapy.

[redacted]

Professor of Respiratory Pathology, [redacted], for Royal College of Pathologists.

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

Name	[redacted]
Role	Senior nurse
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

My mum who is 52 years young was diagnosed with NSCLC in July 2015! This came as a massive shock to all of us as a family. Mum has had chemotherapy and radiotherapy, she was put on a trial for nivolumab, but due to not being enough cancer cells in her biopsy to test they removed her from the trial! Mum wasn't given a second biopsy - apparently "there's no point" we need to try - as a nurse whom follows the NMC guidelines "to do no harm" not re -biopsing my mum, who again is a fit 52 year old, just on the basis of "we might not get any cells" this is disgusting and my mum has been let down by the system! I can't understand why nivolumab isn't available already for cancer sufferers , it has been researched and evidence has proven it actually has a better outcome in terms of symptom control and quality of life.

This past year I have watched my mum,Who was vibrant, energetic, full of life woman decline into something I cannot recognise, I'm an only child so am very close and reliant on my mum. Please do the right thing and make this available for her and many others, all she wants is to be able to speaks the time she has left with better control of her symptoms and possibly more time with her loved ones. I as a nurse have given so much and now it's time that my mum and my family get what should already be available to us.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	

Conflict	No
Notes	

Comments on individual sections of the ACD:

It's disgusting that a drug that could help so many people is available to so little. I really don't understans what makes people think they can play God! Big scientist and money makers don't get to decide if my aunt is here at Christmas or not! Maybe it's time you should stop looking at it from a financial point of view. Over the past year, I've watched my aunt lose her hair, hearing, eyesight and even mobility for a while. I watched my cousin turn from a woman into a girl dependant on anti depressants and terrified of losing her mum. What gives anyone the right to take my aunt away from me when there's a way to save her? What if it was your mum, or brother, or daughter? I'm sure it'd be available then.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Parent
Other role	
Organisation	
Location	
Conflict	No
Notes	

Comments on individual sections of the ACD:

My daughter has just received the devastating news that she has been denied the new treatment of Nivolumab for the treatment of her cancer, as I believe 50% of people have. My daughter was diagnosed with Lung and secondary brain tumours on July 7th 2015 (inoperable). Since then, she has undergone chemotherapy, which had disastrous effects on her. I watched my daughter go through hell. The chemo has left her with permanent hearing loss, and now she faces the prospects of having another course chemo or to leave it and see how it goes. What a choice!

I think this is a disastrous decision you've made, not only for my daughter but many people. I think it makes a nonsense of all the hard work that was put in by doctors and scientists to bring to the for front new medication that can help those with life threatening diseases.

Section 1 (Appraisal Committee's preliminary recommendations)	

Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I have worked full time since I was 15, I am now 61 and have paid full NI contributions and tax all that time and believe we should be able to access the best available treatment through our NHS.

My healthcare policy will not pay for Nivolumab after the 12 month period which finishes on November 9 2016 and I am terrified now as to what will happen regarding my Tumour.

I really hope something can be achieved with BMS so this drug can be made available through the NHS. I had 6 months of Chemo for Lung cancer and it didn't really help and nearly killed me twice but then I was able to have Nivolumab for 12 months through my companies healthcare policy and it has been so effective with little or no side effects and I have now been able to return to work. I think this will replace conventional Chemo in a vast number of cases and I don't need any other drugs to combat the horrible effects of chemo and I don't need any after care at home so I believe that it can be cost effective and if some kind of compromise can be reached I'm sure that BMS could recover their expenditure many times over.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7	

(Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: Why is it that the Scots can be more enlightened than us when it comes to medical care? I appreciate that the drug is probably very expensive, but if it gives people more time to spend with their families, then it should be made available.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Life is too precious to be considered in monetary terms. Please go ahead and approve the introduction of drugs that can and will prolong life.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	

Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Please make your decision based on facts and not cost. Why should people suffer and be denied a chance to recover or live longer because of cost. If there is hope, no matter how small, then give it. Surely to deny people a fighting chance is unethical and depriving them of their human rights. Please help the suffering of cancer patients and the suffering of their families that have to watch them die. It is sadly already too late for sum but not too late for many. Thankyou for listening, [redacted]	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: My sister has lung cancer and has had some treatment, privately funded. This was successful as far as it went, but she now needs further treatment. This drug, nivolumab, has been passed for use with other cancers, and is available in Scotland. why is it not available for lung cancer patients in England?	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	

Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Having lost my cousin to this terrible disease, I feel very strongly about this petition and believe that it should be available to anyone who's suffering now and in the future. My cousin [redacted] was only 48 years old with 3 young children and had never smoked in her life. She only lasted 3 months after her diagnosis and at the time there was nothing we could do to give her and her family more time or any hope. I know this drug might not help everyone but when there is a possibility then how can you not make this drug available. I really hope you can look deep in your hearts and empathise with all of us who have suffered and are suffering now and say Yes to allowing this drug to be prescribed. It's a little bit of hope in a pretty hopeless situation and it could save lives than mean the most to so many people. To know that [redacted] could be one of the last to lose her life could make me smile when I think of her and say 'we're beating it now honey'

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	[redacted]
Other role	
Organisation	

Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: Please make this available for everyone who will benefit, imagine if it could benefit you or a member of your family, but it wasn't available to you!! Everybody's life is precious so please don't discrimate!	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Relative of a lost cancer sufferer
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD: I lost my 57 year old sister to lung cancer last year and I believe that anything that could save a life or buy time should be offered the treatment regardless of anything.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Director

Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Make this drug available for lung cancer, it's a no brainer.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: This drug is a one of a only a few very useful treatments in what is a difficult to treat condition. It prolongs life and will enable improvement in quality of life. I hope NICE will enable this drug to be prescribed by oncologists asap.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public

Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Please consider making the drug available on the NHS, it saddens me that this treatment is available but it cannot be used by those who need it most.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: As a tax payer i cannot emphasise enough that I would consider it a good use of public money to invest in this drug that could extend the life of patients with this format of cancer. I recently lost my mother to this type of cancer and without the funding for drugs such as this one, companies wouldn't invest in research. The hope such medicine can give is priceless and although cost must be a consideration for this common cancer it is my opinion that this is worth the investment.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	

Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

It is vital to understand that this disease can happen to anyone smokers or not lungs need as much care as hearts which can also be due to smoking or not so as heart meds are available in abundance so should effective lung meds to give a better chance quality of life and be more cost effective in the long run as some people can

For the want of a better word 'linger' and care can be excessive by trialling this then maybe the mind and body will except they have been given a good chance more quality time and will be at peace after that special time given

No one could be that conceited to say this may not happen as evidence can then be reviewed which nice is supposed to be about so just do it and see then review

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

If nivolomab can help people recover and / or have a better quality of life then it should be used. Why have a drug that works if it's not allowed to be used, simply because of the cost? It is available for use in Scotland - it is unfair that patients are currently denied access to this potentially life extending drug elsewhere in the UK.

Section 1 (Appraisal Committee's preliminary	

recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I would wish to add my comment in support of using this drug in the fight against cancer.

I speak as someone who personally was diagnosed with Lymphoma three years ago at the age of 60. The awful realisation that you have been given this diagnosis affects not only yourself but every member of your family and work colleagues. The stress is enormous and my daughter; aged 31, has just recently had a smear and found 'abnormal' cells. She has been scheduled for surgery now on 3rd November 2016. The whole family are once again under enormous stress awaiting the outcome of this surgical procedure. Any drug that can be used to fight this awful disease must be given at the first opportunity as time is crucial in cancer.

I would urge the Committee to please allow the use of this drug and thank the Committee for taking my comments into consideration.

Everyone deserves the opportunity of additional time that may result from treatment with this drug.

[redacted]

27/10/2016.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	

Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: Patients deserve the chance this 'wonder drug' will give them. It seems especially unfair for it to be available to those so close to us just over the boarder in Scotland and not yet here. Please allow this drug to do its job and make a difference to the people who need it most. Many thanks for your consideration.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Each and every human being should be given this drug should it be needed, everyone needs to be given the best chance to live. Money or Life, which is the most important? The answer to this is LIFE !!!!! It's not just the person's life at stake, but that of the loved ones involved.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	

Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD: Great Britain comprises England, Wales, Scotland and Northern Ireland. It therefore seems illogical that this medication is available on the NHS in Scotland but not on the NHS in England and Wales. Why should one geographical area of Great Britain be treated differently, and unfairly, to other parts? What's appropriate for Scotland is equally appropriate for England and Wales and vice versa. Please approve nivolumab for use by the NHS in England and Wales.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	

Comments on individual sections of the ACD: How can NICE justify their position when this drug is available in Scotland. Lives should be treated with equal value. People should not be subjected to post code lotteries when life prolonging/saving medication is required. NICE management should take a hard look in the mirror and ask themselves this " What if this were my wife, husband, mother, father, child' It's

time for NICE to do the right thing!	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: This drug is approved for use in Scotland. You would need to refute their reasons for approving it , should you decide not to make it available to people in England. Please consider long & hard whether anyone could benefit. Medicine is an uncertain science & you should err on the side of the patients& humanity.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	
Other role	

Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

From scanning through the Appraisal consultation document relating to Nivolumab, it seems to me, as a member of the general public, that much of the content is a critique of the evidence provided by the company. It seems that this approach could obscure the merits of what is considered to be an innovative treatment.

I would ask the committee to take note of the fact that Nivolumab has apparently been approved for use in the USA, and in certain circumstances in Scotland and possibly also in other countries. NICE should consider the reasoning that led to the approval of Nivolumab in other jurisdictions. There appears to be a danger of England and Wales falling behind other countries as regards treatments available and service to patients.

The focus of NICE should ultimately be to benefit the public at large. A petition in support of availability of Nivolumab has received over 173,000 signatures, but it is understood that NICE has declined to discuss the position with the organisers of the petition. I would ask the committee to consider whether they should be more open to discussion, and to give great consideration to the effect of their decisions on the public.

Given the very significant effect of NICE decisions on the life expectancy of individuals, democratic principles require that NICE should be willing to discuss their recommendations, and to take note of views put forward by others, particularly where, as in the case of Nivolumab, a very large petition demonstrates the concern of the public at large with regard to this issue and other jurisdictions have approved the treatment for use. This democratic principle is not satisfied by the publication of the Appraisal consultation document, where the information provided is extremely technical in nature and, as noted above, is apparently focussed to a significant degree towards a critique of evidence supplied by the company.

In the case of a treatment such as Nivolumab, which is considered to be innovative, there is a need for the treatment to be made available on a provisional basis, pending more detailed evidence. The treatment should be considered for availability under the Cancer Drugs Fund and, pending this, it should be available on a provisional basis.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	

Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Please review this drug to help lung cancer suffers have more life	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I support the approval of Nivolumab, as it will give valuable time for cancer sufferers. I understand the cost implications, but surely people deserve any chance of life. Perhaps savings could be made in the NHS for cosmetic type treatments and drugs - they are not necessary.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	

Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I sincerely request that your consultation committee takes the request of thousands like myself who have signed [redacted]'s petition, very seriously indeed. It seems bewildering that here in the 'United Kingdom' that Scotland is able to prescribe Nivolumab when we in England cannot. The drug has had glowing reports of efficacy. We spend so much on frivolous items , please make this drug available. There is hardly a family in the land (the WHOLE LAND) who has not been effected with cancer and our air pollution has seriously contributed to many of it's forms. I hope you will do the right thing by [redacted] mother and thousands like her.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD: We need to take opportunities to sustain human life comfortably. Withholding this medication for the positives that it can provide is surely against individual human rights and advancement of medical practices nationwide.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2	

(The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Everyone should be given the opportunity to have a drug that could improve their quality of life. It shouldn't ever come to down to money. Some common sense should be considered here. put themselves into the shoes of the person affected and they may well begin to see sense	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: If Nivolumab can save lives it should be made available to those people who so desperately need it. Try to imagine what you would want if someone you loved dearly could live longer because of it. If you're totally honest there is only one thing you could possibly want.	

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Please make this Nivolumab medicine available for those people who are life-threateningly ill and also for the lives of their loved ones that are so profoundly affected by the illness they all forced to cope with each day. This medicine being made available could mean so much to so many peoples lives. When someone has lung cancer it not only affects the person that has the cancer, but also all of the people who love and care deeply for that person. And the possibility that they can lose someone they love dearly when the person they love could have their life saved by a particular drug or medicine is such a devastating thought. Thank you for listening.

Yours faithfully

[redacted]

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Life is so precious, every day counts. Anything that can give a person more days in their life MUST be made available, it's why we have science and research, otherwise what's the point?	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD: To spend money and time on cancer research and then not approve the drugs that come from it makes no sense .	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review	

of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: This drug is a breakthrough in cancer treatment, allowing immune cells to attack cancer. It has been approved in the U.S. and Japan. It should be approved in the UK to help current cancer patients and to advance the development of this new series of drugs.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: There has been very little progress in the treatment of lung cancer for far too long. Nivolumab has advantages over all other treatment options and that is progress which should be made available in England and Wales to suitable candidates. Re concluding remarks of Bristol of Myers Squibb (BMS) . Any treatment that offers reduced toxicity to paitents during treatment has surely to be a key advantage that is better for the paitent but also reducing costs that would otherwise have been incurred counteracting the toxicity of standard treatments and the added advantage of possibly a better quality of life that may be extended for longer.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

iven that Nivolumab has already been available in the NHS through the EAMS and that a patient access scheme provided a level of discount for this important drug which is described as innovative, I am utterly dismayed that the cost and pricing model for the drug production has not been reviewed in more detail. In this day and age, we in the private sector organizations (regardless of what services we offer or what we manufacture), have been forced to review our internal processes and our resources in order to cut costs. This has resulted in a less costly provision of goods and services where outsourcing to low cost resources for non-skilled work has been adopted. I would ask therefore, that the committee attempt to negotiate and agree a better pricing structure with the drug company for the supply of this drug and a more transparent cost model for its production, rather than dismissing this important drug on the basis of cost.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No

Notes	

Comments on individual sections of the ACD:
I have read the document with care and considered the Committee's findings. I see a great deal of genuine evidence presented, and a great deal of careful weighing of the financial costs of one novel treatment (nivolumab) versus others that are currently available. One thing that is nowhere evident is any empathy with sufferers and their families, for whom this represents a "last chance" of putting the disease into remission, or at least extending not merely the length, but also the quality of life of the victims. No price on earth can be put on the chance to have a little more time with those people who matter most to us. I sincerely hope that none of the Committee ever find themselves in the position of the families for whom they are "not minded" to approve the drug. At the same time, I appreciate that health funding is not unlimited and that approval of this drug may take finances from somewhere else. In the best British tradition, then, I urge a compromise - let the drug be licensed for a trial period so that the manufacturer's claims can be tested in the real world. The Committee made much of the fact that there was no evidence of appropriate comparative trials - if the drug is not licensed in the UK, how can such trials ever take place? While the experts deliberate, victims suffer and die - perhaps needlessly, perhaps not. Please, give this drug a fair trial.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:
my wife has lung cancer which was treated wrongly and if nothing is done I will sue the NHS
I am contacting you for your assessment on non small cell lung cancer using nivoluminab and if you decide this is not appropriate for then the the row over herceptin will be a sideshow will be a sideshow compared to the row this will bring even calling for nice be disbanded

Section 1 (Appraisal Committee's preliminary recommendations)	

Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD: Based on what Ive read on the subject it seems only logical that since Nivolumab is given to patients in Scotland, it should be given to patients in need in Wales and England too. After all part of the same United Kingdom.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: My mother currently has stage IV NSCLC and was on a trial randomly assigned standard platimum chemotherapy rather than nivolumab. At the time my mother was told (by her oncologist) that nivolumab was a better option in terms of outcome, and side-effects. Now that the chemotherapy has failed to work and subsequent	

radiotherapy has left my mother extremely tired, what I've noticed is that since her diagnosis there has been very little time during which she could live her life at anything like a normal level. For people with exceptionally low life expectancy, a small number of higher quality months are of dis-proportionally high value, not just for the person themselves, but also for their family. I take it that this is obvious enough. Have you, or will you, account for this?

An example to make this point clearer: extending a (relatively high quality) life expectancy (at diagnosis) from 30 months, to 32 months is less valuable by far than extending a 2 months life expectancy (at diagnosis) to 4 months.

We're (my mother, my father, my mother's many brothers and sisters, me, and my children) looking down the barrel of there being no quality time left at all, and importantly there has been almost none so far. It looks like this drug has a chance of changing that. Is it worth the cost? You have to decide, but you have to consider the problem properly, not as a straightforward 'cost per month of extra life' type analysis. This particular cancer is particularly nasty, and you must consider what that changes in your standard calculations, when making your final recommendations.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Of the 9.6 million smokers in the UK, there are different rates of smoking among men and women. Action on Smoking and Health (ASH) reported in October 2016 that 20% of men smoke, whereas only 17% of women smoke in the UK. Hence there are aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination on the grounds of gender.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

My mother has stage 4 Lung cancer. I'm outraged and upset at the reason Nice have given to not approve Nivolumab so far.

Why hasn't this decision been made sooner, costs, lack of research, or lung cancer patients aren't worthy enough. Every cancer deserves the same respect and not to be isolated because of lack of resources.

Lung cancer is one of the biggest killers in Britain and it deserves more support.

The effect it has had on my mother and family is devastating and, so upsetting to see my mother starting to loose hope because all that is left is Nivolumab to help.

Please make the right positive decision today.

All cancer sufferers deserve to live as long as they can given them dignity and respect they deserve.

[redacted]

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	m v chopping
Role	Supporter of petition for Nivolumab
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Dear Sir, Madam

I would like to add my support for a fellow citizen in England whose mother has lung cancer and requires Nivolumab to help her fight against cancer, but because of where she lives the NHS will not provide it for her. I feel we only really understand cancer when we have been through it ourselves, as so many of us are getting cancer we all need to help each other so that we can get a better understanding of cancer and how we can progress to obtain a cure.

Thank you for you time.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Newcastle University

[redacted]

November 3rd 2016

We the undersigned believe that the present guidance as the cost-effectiveness for Nivolumab in previously treated squamous and non-squamous lung cancer does not accurately reflect the scientific evidence.

We believe there are important research questions to be answered about the most effective use of these expensive drugs; in particular which patients are most likely to benefit and what the optimal treatment length should be, and that the National Health Service is an ideal place to perform such research. However these important questions will not be answered by the present approach advocated by NICE, which is not supported by the clinical trial data or scientific opinion.

In particular we wish to comment on the suggestion that any funding through the Cancer Drugs Fund should be restricted to patients where the diagnostic biopsy shows PD-L1 staining of >10% of the tumour cells. This suggestion is not supported by the clinical trial evidence.

In the trial of nivolumab in previously treated squamous lung cancer that led to license (Checkmate 17) there was no evidence of PDL1 status as a predictive biomarker.

In the trial of nivolumab in previously treated non-squamous lung cancer that led to license (Checkmate 57), whilst there was a trend to improved effectiveness with increasing PDL-1 expression, there was no defined threshold. An attempt to define a threshold on retrospective modelling of sub-group analyses of cohorts (when there are small numbers in each group) is not valid and would not be acceptable if used in support of a funding application or in devising clinical guidelines.

We also believe the committee has not fully considered how this decision could be implemented in the NHS. Many patients with thoracic malignancies will not have suitable samples for PDL1 analysis, thus repeat biopsy may be required. That will place our patients at risks of additional procedures and will also put additional strain on respiratory diagnostic services which are already struggling with meeting government targets as to speed of diagnosis and appropriate treatment.

We also do not think that most UK pathology departments are set-up to deliver this. This test requires interpretation by skilled respiratory pathologists employing assays on a validated platform. It is clear that this is not deliverable with the present set-up; this will in particular disadvantage patients diagnosed and treated at some of the smaller cancer units.

We urge NICE to work with Bristol Myers Squibb to come to a solution that will allow cost-effective access to these drugs to the benefit of our patients.

change.org

Petition Starter: [redacted]

Email: [redacted]

Phone: [redacted]

Petitioning:

- National Institute for Health and Care Excellence

Ask: Make lung cancer drug- Nivolumab available for all in England and Wales

Signatures: 95,632

Letter: I'm a nurse and I'm also a proud daughter, of my beautiful mum who is 52 years young. Mum was diagnosed with brain metastases from lung cancer in July 2015 . This diagnosis came completely out of the blue and has sent shock waves throughout our family. Mum has always been very active and to see her change each day is heart breaking, she is my mum and my best friend.

Since diagnosis mum has had chemotherapy and radiotherapy twice, it has kept the cancer under control so far but how long this will last nobody knows. Mum had to stop having chemo due to the effect it has had on her kidneys. But there is a new drug, Nivolumab, called a wonder drug by doctors and it is her only chance of a real difference to how we move forward. It can add years to what at the moment is a poor prognosis. It has been proven to eradicate tumour cells, doesn't destroy normal healthy cells like chemo does, but it highlights those cancer cells that are clever and hide then the immune system attacks those cells.

This drug is a real break through in treatment of lung cancer and skin cancer, it should be made available for every cancer sufferer and should not be based on how much the cost is. As a medical professional I am disgusted that we, and many others, are going through this, fighting for what we deserve, whilst going through the most difficult time of our lives.

NICE are currently deciding whether or not to fund this wonder drug, the decision is expected any time now. So please sign my petition calling on NICE to do the right thing.

Please share with family and friends we need as many signatures as possible many thank you in advance,

Love [redacted]

change.org

Petition Starter: [redacted]
Email: [redacted]

Phone: [redacted]

Petitioning:

- National Institute for Health and Care Excellence

Ask: Make lung cancer wonder drug available in England and Wales
Signatures: 174,083

Letter: Our Mam [redacted] was diagnosed with lung cancer in November 2014. She is a Mother to five of us and has five Grandchildren too. She is a wife, a daughter, a sister, an auntie and a friend to many people.

We all love and care for her dearly and don't want her to die, but she is very poorly and doesn't have the luxury of time. She has gone through chemotherapy twice and radiotherapy. Her oncologist says her only chance to live longer is a drug called Nivolumab. It is proven to give lung cancer patients more time and in some cases eradicate the cancer completely.

Doctors call it "the wonder drug".

It has already been approved for use and in Scotland they are already giving this drug to lung cancer patients. In October 2016 NICE will be making their final decision on whether lung cancer sufferers in England and Wales will receive the wonder drug.

We only have a month. Please sign this petition to help NICE make the right decision.

Thank you so much for taking the time to read and sign!

Her children [redacted]

Executive Summary

Ahead of the next Appraisal Committee Meeting (ACM), Bristol-Myers Squibb (BMS) Pharmaceuticals Ltd would like to present the following document in order to address some of the uncertainties identified in the various appraisal consultation meetings to date and in the most recent Appraisal Committee Document (ACD) published on 14 October 2016.

In order to address these uncertainties, a number of solutions are being proposed to further support the case for the cost-effectiveness of nivolumab in non-squamous non-small cell lung cancer (NSCLC). The first of these is to introduce a revised patient access scheme (PAS); the second is to include results when a 2-year stopping rule is applied; and finally to present scenarios where a credit from melanoma and renal cell carcinoma (RCC) is applied (given that the revised PAS will apply across all 6 licensed indications of nivolumab).

The results for these scenarios are presented to reflect both the original assumptions submitted by BMS and the assumptions chosen by the Evidence Review Group (ERG). BMS and the clinical community maintain that the ERG have severely underestimated the long-term overall survival (OS) of nivolumab in its indicated patient populations, a sentiment further supported by more mature 5-year data from the CheckMate 003 trial. Data from this trial shows evidence of a [redacted] in OS from [redacted] at a survival rate that is [redacted] than the original BMS extrapolation. The OS predicted by the ERG does not reflect this and instead assume a constant mortality that is inappropriate for immuno-oncologic therapies. In order to accommodate the potential uncertainty in the committee's mind, intermediary scenarios have been provided. The ICER associated with the intermediary curve is £47,684 per QALY for non-squamous NSCLC. These results demonstrate that nivolumab is a cost-effective use of National Health Service (NHS) resources in patients regardless of PD-L1 expression.

Adoption of nivolumab for the treatment of NSCLC would represent a step-change in advancing the management of this life-threatening condition and improving long-term survival. Nivolumab for this indication has already been recommended for use in Scotland by the SMC. Despite the recent NICE approval of another checkpoint inhibitor, pembrolizumab, for patients with NSCLC whose tumour expresses PD-L1 at ≥1%, and have had at least one previous chemotherapy regimen. There still exists a clear unmet need, in the paper published from Keynote 010 (Herbst et al) the number of patients that were PD-L1 positive ≥ 1% was 54% of the tested population. Therefore BMS believes approximately 45% of patients would be ineligible for treatment with pembrolizumab, based on a negative or absent test result, and so would be potentially treatable with nivolumab.

PD-L1 Subgrouping

As noted in the ACD published in October 2016, the appraisal committee made differential recommendations for nivolumab based on a patient's PD-L1 expression. BMS believes that it is inappropriate to make recommendations for nivolumab based on PD-L1 expression and that NICE exceeded its powers by seeking to define a subgroup in this manner.

There are a number of reasons why we believe this to be the case:

- The registration phase 3 studies for both indications of nivolumab in NSCLC - CheckMate 057 (non-squamous) were not powered to show a difference between the PD-L1 subgroups; so any conclusions are inherently uncertain.
- The European Medicines Agency assessed the benefit-risk profile of nivolumab as being favourable in all patients, regardless of PD-L1 status.
- PD-L1 is an imperfect predictive biomarker. Testing methodologies are still being developed, and there is no single standardised test routinely used by the NHS. The tests have a high positive predictive value but a low negative predictive value.

For more information, please see the ACD responses submitted by BMS (dated 4 November 2016) where many of these issues, as well as others, are presented.

Revised Patient Access Scheme

Analyses in this proposal have used a revised PAS, which we expect to be swiftly approved by the Department of Health. This simple confidential discount then will be offered to all patients in all licensed indications of nivolumab at [redacted] and will be implemented once this appraisal has been recommended for the two NSCLC indications under review.

Two-year Stopping Rule

In the key phase III trial, Checkmate 057, demonstrating the clinical efficacy and safety of nivolumab monotherapy in pre-treated advanced non-squamous NSCLC, patients continued to receive study drug until disease progression, or unacceptable toxicity, as per protocol. UK and international expert clinical opinion has confirmed that for those patients who have responded to nivolumab, treatment to progression will not be reasonable in routine clinical practice, and that stopping therapy at an appropriate time point should be considered.

Checkmate 003 explored various doses of nivolumab across a range of tumour types. This study included 129 pre-treated NSCLC patients. The study protocol specified a stopping rule for discontinuation of therapy at 96 weeks (1.8 years). The majority of patients who achieved complete or partial response before 96 weeks, maintained their response. This treatment pattern is confirmed across all the tumour types and all doses of nivolumab in the study. Based on this study, UK clinicians agreed that limiting the maximum duration of treatment could be supported. Further to this, the SMC have recommended nivolumab in the treatment non-squamous NSCLC under the condition that a 2-year stopping rule is applied.

In addition, as discussed in previous correspondence, BMS are investigating a one year stopping rule in study Checkmate 153. This is a phase IIIB/IV safety study in which patients with stable disease at 1 year are randomised to stop treatment (with the option of retreatment on progression) or standard treatment to progression.

As can be seen from the recent Final Appraisal Determination (FAD; TA428) for pembrolizumab issued on 2nd December 2016, a stopping rule can be applied for therapies within routine baseline commissioning. In support of this NHS, England provided the following comment:

'it was confident that a 2-year stopping rule would be acceptable to both patients and clinicians and would be implementable.'

Finally, in the recent appraisal of nivolumab for melanoma by NICE (TA 384), the Institute noted uncertainty of optimal duration of treatment, and commitment to re-review the evidence in 2 years when it may be more feasible to clarify optimal duration of treatment. It is worth noting that 2 years is equivalent to 104-weeks of therapy. However, within the nivolumab Checkmate-003 study a 96-week stopping rule was applied. This difference of 8 weeks (4 doses) will increase the cost of nivolumab, and so represents a more unfavourable scenario for nivolumab from a cost-effectiveness perspective.

Melanoma & renal cell cancer 'credit'

At the nivolumab Appraisal Committee Meeting in October 2016, the committee discussed whether the impact of wider benefit to the NHS could be taken into account because the simple discount agreed to in the PAS would apply across all indications.

This also was acknowledged in the recent appraisal of pembrolizumab and included in Section 4.18 of the FAD for pembrolizumab in NSCLC (Technical Appraisal No. 428), which states,

"[the committee] was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications."

Nivolumab has already been appraised and recommended by NICE for melanoma (Technical Appraisal No. 384 and No. 400) and RCC (No. 853). All of these were recommended with a discount of less than [redacted] (see Table 1).

Table 1. Credit Gained From Existing Indications

Indication of Nivolumab	Cost-effective PAS Level	Proposal Selling Discount	'Credit' Percentage
Melanoma	0%	[redacted]	[redacted]
RCC	[redacted]	[redacted]	[redacted]

PAS = patient access scheme; RCC = renal cell carcinoma.

Under the current proposal, both melanoma and RCC would be available with a [redacted] discount, resulting in a lower treatment costs for these indications. To account for these savings, the melanoma and RCC cost-effectiveness models were run at the cost-effective PAS levels (0% and [redacted], respectively) and then again at [redacted]. The difference in cost per melanoma or RCC patient treated with nivolumab was then subtracted from the incremental costs in the models used to derive the incremental cost-effectiveness ratios (ICERs) for the NSCLC indications of nivolumab.

Impact of the Melanoma and RCC Credit on the BMS and ERG's ICERs

Table 2 represents the ICERs for the BMS-preferred assumptions and the ERG-preferred assumptions in which both the revised PAS and the 2-year stopping rule are applied. The main difference between the two approaches is the way in which each has extrapolated the long-term survival. Further details on how the modelling assumptions differ can be found in Appendix A. In addition, Table 2 shows the reduction in ICERs when the melanoma and RCC credit are applied.

Table 2. ICERs With Revised PAS and 2-Year Stopping Rule with and Without Melanoma and RCC Credit Applied

Modelling Assumption	Indication	ICER (Without Credit)	ICER (With Credit)	Impact of Credit
Non-squamous	BMS	£47,612	£42,399	–£5,213
	ERG	£76,893	£67,908	–£8,985

BMS = Bristol-Myers Squibb; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio.

The Intermediary Curve

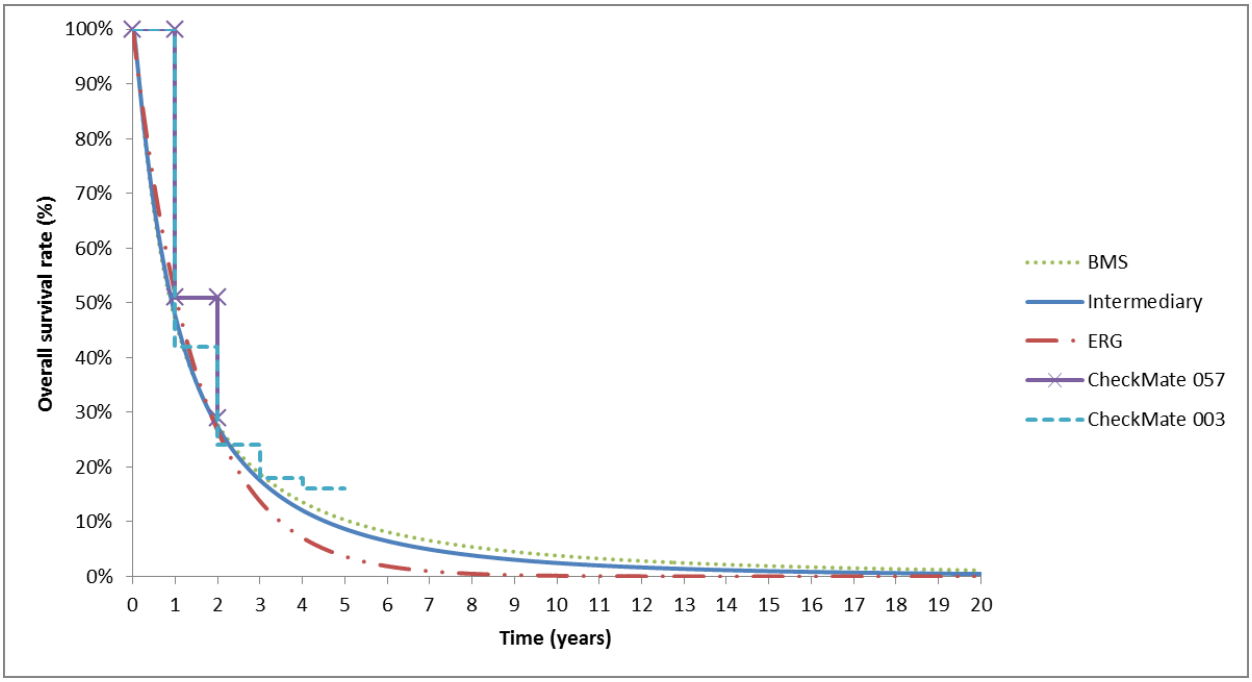
The appraisal committee preferred the ERG's approach to modelling the long-term OS. BMS believe this approach is not valid because it does not represent a fair set of assumptions that one would expect to see in clinical practice. BMS believe that the steps taken in the company submission to identify the most appropriate extrapolation function based on the guidance from NICE's Decision Support Unit and from Royston and colleagues (see Appendix B) led to the most appropriate extrapolation functions being included in the company submission. In order to further validate this approach and to disprove the ERG's approach, we present the data from the longest current 2L NSCLC clinical trial, CheckMate 003. The time points of 4 and 5 years are now available; and, as can be seen from **Error! Reference source not found.**, show a [redacted] We feel that the results from this trial are generalisable as the populations have comparable characteristics (similar age – early 60s, similar percentage of PS 1 patients - 78% and patients that have had previous platinum therapy – 99-100%) to those populations in the two phase 3 trials as well as in UK clinical practice. This data show a survival rate that is greater than the original BMS extrapolation. The OS predicted by the ERG does not reflect this and instead assumes a constant mortality rate that is simply not logical from a biological perspective and therefore inappropriate for immune-oncologic therapies.

BMS consulted a few physicians to gain their opinion on the likelihood of a plateau for long term survival for nivolumab in pretreated lung cancer as has been seen in other tumours. They felt that the ERG curve was unrealistic and did not reflect what they would expect to see in the real world from NSCLC patients treated with immunotherapy. The ERG's clinical expert (for these appraisals) also disagreed with the ERG's extrapolation and confirmed that immunotherapies work using a different mechanism of action and simply cannot be modelled by using the same assumptions of long-term effects from chemotherapy. We understand that they will further discuss this over coming weeks and are likely to submit a letter with signatures of a number of leading oncologists to NICE reflecting their independent viewpoint in the coming weeks.

Given the difference in preferred methods for predicting long-term OS, BMS have further investigated the selection of survival extrapolations for nivolumab in squamous and non-squamous NSCLC. Based on this, a third scenario is presented that provides the advisory committee with an intermediary curve that represents a scenario in which the long-term OS lies between the two approaches (BMS's and ERG's) already discussed. In addition to representing an in-between scenario, this third scenario was based on extrapolations that fulfilled additional criteria put forward by the ERG for being a valid extrapolation. These criteria were: predicted mortality should always greater than all-cause mortality and OS should always be greater than progression-free survival (PFS).

The intermediate curves can be seen in and Figure 1 for non-squamous NSCLC. The invalid curves for both indications of NSCLC that were tested are presented in Appendix C.

Figure 1. Non-Squamous Overall Survival Curve Options



BMS = Bristol-Myers Squibb; ERG = Evidence Review Group.

The OS rates from the three clinical trials, as well as the three modelling approaches at various time points, are presented in Table 3.

Table 3. Overall Survival Rates From the Three NSCLC Clinical Trials and the Three Modelling Approaches

		Proportion Alive						
Data Source	**Curve**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**	**10 years**	**15 years**
Non-squamous								
CheckMate 057		51%	29%					
CheckMate 003 (non-squamous and squamous)		42%	24%	18%	[redacted]	[redacted]		
Model estimates for nivolumab OS	BMS Log-normal	46.78%	27.78%	18.75%	13.61%	10.35%	3.83%	1.93%
	Intermediary Generalised gamma	47.64%	27.35%	17.58%	12.08%	8.70%	2.47%	0.98%
	ERG Exponential	51.61%	26.63%	13.74%	7.09%	3.66%	0.13%	0.00%

BMS = Bristol-Myers Squibb; ERG = Evidence Review Group; OS = overall survival.

Using an intermediate OS curve instead of the BMS-preferred assumptions increases the ICERs, and as can be seen from visual inspection lie between the BMS and ERG curves. It is worth noting that all these curves are [redacted] than the actual data seen at years 4 and 5 of CheckMate 003. Using the generalised gamma curve for the overall survival, all valid combinations for PFS and TTD were identified are presented below (table 4). A list of all combinations that were deemed invalid from a statistical and/or clinical perspective is presented in Appendix C. The average ICER was £47,684 for non-squamous NSCLC.

Table 4. Extrapolation Scenarios for Non-Squamous NSCLC

OS	PFS	TTD	ICER
Generalised gamma	Weibull- PFS		£48,643
Generalised gamma	Gamma- PFS		£50,235
Generalised gamma		Weibull- TTD	£48,555
Generalised gamma		Gamma- TTD	£50,334
Generalised gamma		Log-logistic- TTD	£40,654
		Average ICER:	**£47,684**

NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

BMS are aware of the NICE appraisal of pembrolizumab in advanced pretreated NSCLC (TA 428). For consistency and given that both treatment options relate to similar patient populations, the comparators in both appraisals should be the same. In fact, nintedanib plus docetaxel is included in the nivolumab appraisal but not the pembrolizumab appraisal. BMS raised this during the consultation, requesting that the comparators be consistent. This point was discussed at the appraisal committee meeting for Pembrolizumab on October 26th, and the committee decided that nintedanib plus docetaxel should not be a comparator in that appraisal. The ICERs presented in this document are therefore only versus docetaxel.

Future Long-Term Data

As discussed above, the main uncertainty regarding nivolumab's cost-effectiveness is the long-term extrapolation of OS. There are five ongoing BMS-sponsored studies, the dates of which are provided in Table 5. The divergence between the BMS and ERG extrapolation methods occurs at 2 years. It is expected that additional data cuts from CheckMate 017 and CheckMate 057 will further demonstrate the validity of the BMS approach.

Table 5. Summary of Key Clinical Trial Planned Publications

	Time Point (Months)				
Trial	**12**	**24**	**36**	**48**	**60**
CheckMate 003 (N = 129)					[redacted]
CheckMate 063 (N = 117)			[redacted]	Not planned	Not planned
CheckMate 017 (N = 272)			[redacted]	[redacted]	
CheckMate 057 (N = 574)			[redacted]	[redacted]	
CheckMate 153 (N = 531)	[redacted]	[redacted]	Not planned	Not planned	Not planned

As noted above, in the recent appraisal for melanoma by NICE (Technical Appraisal No. 384), the institute concluded there was uncertainty regarding the optimal duration of treatment and committed to a re-review of the evidence in 2 years, when it might be more feasible to clarify optimal duration of treatment. Table 6 is a summary of the estimated dates for the re-reviews of the currently licensed indications of nivolumab. The estimated dates provided for the re-review of the 2 NSCLC appraisals of nivolumab coincides with when we would expect to have the 4-year OS data to further validate our own approach. This also would be in line with the recent recommendation for the pembrolizumab appraisal (Technical Appraisal No. 428), which also has a 2-year review planned.

Table 6. Estimated Dates for the Nivolumab Technology Appraisals Conducted Thus Far

NICE Technical Appraisal No.	Indication of Nivolumab	Date for Re-review
384	Melanoma (monotherapy)	February 2018
400	Melanoma (regimen)	May 2018
417	RCC	October 2019
811	NSCLC (non-squamous)	Approximately June 2018[a]
900	NSLCL (squamous)	Approximately June 2018[a]

BMS = Bristol-Myers Squibb; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; RCC = renal cell carcinoma.

[a] BMS proposed dates in order to incorporate the 48-month OS data from CheckMate 017 and CheckMate 057 (Table 6).

Conclusion

Adoption of nivolumab for the treatment of non-squamous NSCLC would represent a step-change in advancing the management of this life-threatening condition and improving long-term survival. Despite recent recommendations in this disease, there still remains a clear unmet need for those patients that are PD-L1 non-expressers (<1%), those that are unable to be tested for PD-L1 or those patients that simply do not have the time to wait to be tested. With application of the various pricing solutions being presented by BMS:

- Revised patient access scheme (PAS);
- 2-year stopping rule is applied;
- Credit from melanoma and renal cell carcinoma (RCC) is applied

More mature data from CheckMate 003 showing [redacted], as well as the overwhelming clinical opinion that the ERGs assumption of constant mortality risk for patients on nivolumab (exponential curve) is simply incorrect. With this in mind, an intermediary curve is presented in order to afford the committee the reassurance that there are a number of approaches to modelling the overall survival which still demonstrate the cost effectiveness of nivolumab. Results of these scenarios are summarised in table 7 below.

Table 7. ICERs with Revised PAS, 2-Year Stopping Rule and Melanoma and RCC Credit

Indication	Modelling Assumption	ICER
Non-squamous	BMS	£35,907
	Intermediary	£47,684
	ERG	£67,908

Appendix A

Table A-1 and Table A-2 shows the utility data and extrapolation functions used in BMS's approach, ERG's approach, and the intermediary scenario presented in this proposal for squamous and non-squamous NSCLC, respectively. With regards to utility values for non-squamous NSCLC the appraisal comity agreed that the true values for utility value for progressed disease would be between the BMS proposed 0.657 and the ERG proposed 0.480 and thus 0.5685 has been used for all scenarios presented as part of this proposal.

Table A-1. Squamous NSCLC Model Assumptions

	BMS	Intermediary	ERG
OS	Log-logistic	Generalised gamma	K-M data followed by exponential
PFS	Nivolumab: 1-knot spline hazard Docetaxel: Log-normal	See table 4	Exponential
Utilities	Progression-free = 0.693 Progressive disease = appraisal committee agreed to 0.509	Progression-free = 0.693 Progressive disease = appraisal committee agreed to 0.509	Progression-free = 0.693 Progressive disease = appraisal committee agreed to 0.509

BMS = Bristol-Myers Squibb; ERG = Evidence Review Group; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival.

Table A-2. Non-squamous NSCLC Model Assumptions

	BMS	Intermediary	ERG
OS	Log-normal	Generalised gamma	K-M data followed by exponential
PFS and TTD	Log-normal TTD TTD to model all outcomes and costs	See table 5	K-M data followed by exponential PFS to model health states TTD to model treatment-related costs and AEs
Utilities	Progression-free = 0.713 Progressive disease = appraisal committee agreed to be between 0.657 and 0.480 (i.e., 0.5685)	Progression-free = 0.713 Progressive disease = appraisal committee agreed to be between 0.657 and 0.480 (i.e., 0.5685)	Progression-free = 0.713 Progressive disease = appraisal committee agreed to be between 0.657 and 0.480 (i.e., 0.5685)

AE = adverse event; BMS = Bristol-Myers Squibb; ERG = Evidence Review Group; K-M = Kaplan-Meier; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

Appendix B

The primary data source for the economic models were patient-level data from the CheckMate 017 and CheckMate 057 clinical studies. The follow-up period in both these trials was shorter than the required length of the economic analysis (a lifetime equivalent), and extrapolation of the time to treatment discontinuation (TTD) or PFS and OS data was required for the partitioned survival (area under the curve) approach. This involved identifying parametric survival models for both OS and TTD or PFS.

The guidance from the NICE Decision Support Unit and from Royston and colleagues was followed to identify the best-fitting parametric survival model for OS and TTD. In summary, the steps required included:

1. Testing the proportional hazards effects assumption: the log-cumulative hazards, log-cumulative odds, and standardised normal curve plots were assessed to determine if the data from CheckMate 017 and CheckMate 057 indicated proportional effects. This was done by visual inspection to determine if the survival curves for the nivolumab and docetaxel arms were parallel.
2. In the event proportional hazards effects held, a comprehensive range of parametric survival distributions was explored. These included the standard exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma models, as well as a series of flexible spline-based models.
3. In the event proportional hazards effects did not hold, both independent-survival models and single-survival models, adjusted for shape and scale, were assessed.
4. Within the various parametric survival distributions explored (whether single or independent models), the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics were assessed to identify the best-fitting survival models.
5. Finally, the choice of parametric model was validated for clinical plausibility of both short-term and long-term extrapolations. This involved eliminating the combination of curves that crossed and thus would be deemed clinically implausible.

The final choice of parametric survival model adopted for the base-case model was a balance between statistical fit (as per AIC and BIC values); comparable survival rates to CheckMate 017 and CheckMate 057, respectively, within the period when patient-level data were available (18 months); and long-term clinical plausibility of the extrapolated model, based on clinical opinion that was confirmed with the clinical consensus statement recently signed by various lung oncologists (see page 9). The long-term clinical plausibility of the

extrapolated model also was based on validation of extrapolation functions against available nivolumab clinical study data with longer follow-up, i.e., the CheckMate 003 study, for which we now have 5-year data. For the full description of the rational for selection of curves in each step, as well as of considerations taken for selecting the final set of curves, please refer to the company submission for both indications.

From following the steps 1 through 5, the following curves were selected for each indication:

- Non-squamous NSCLC
  - OS: log-normal
  - TTD (used to represent both TTD and PFS): log-normal
- Squamous NSCLC
  - OS: log-logistic
  - PFS for nivolumab: 1-knot spline hazard
  - PFS for docetaxel: log-normal

Appendix C

To further investigate the selection of extrapolations for nivolumab in squamous and non-squamous NSCLC, given the discrepancy between BMS- and ERG-preferred extrapolations, additional analyses were run to identify an intermediary curve per indication. This curve represents a scenario in which the long-term OS lies between the two approaches already discussed. In order to identify this intermediate curve, additional combinations of extrapolation functions fitted to OS and TTD or PFS were investigated. In addition to representing an in-between scenario with regards to survival, the selection of curves also was based on extrapolations fulfilling additional criteria put forward by the ERG for valid extrapolations. These criteria were: predicted mortality should always greater than all-cause mortality and OS should always be greater than PFS.

A combinations of curves were tested for squamous NSCLC and non-squamous NSCLC. The curves deemed invalid based on the above criteria and are summarised in Table C-1 and Table C-2.

The intermediate curves selected for both squamous and non-squamous NSCLC were generalised gamma for OS. Generalised gamma was selected for OS for non-squamous NSCLC because it is an intermediary between the BMS and ERG approach and fulfils the above criteria.

All combinations that included exponential curves were excluded because of the more mature CheckMate 003 data that shows evidence of a clear plateau, as well as the clinical consensus statement that challenges the ERGs approach to using exponential to model immuno-oncologic therapies.

Table C-1. Invalid Extrapolations for Squamous NSCLC

OS	PFS	Notes
Generalized gamma	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Exponential	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause

OS	PFS	Notes
Gamma	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Generalized gamma	OS and PFS cross in the Nivo arm OS less than all cause
Gompertz	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Generalized gamma	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot hazard	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Spline 1 knot odds	Generalized gamma	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Generalized gamma	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Generalized gamma	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Gompertz	Exponential	OS less than all cause
Log Logistic	Exponential	OS less than all cause
Spline 1 knot odds	Exponential	OS less than all cause
Spline 2 knot odds	Exponential	OS less than all cause
Exponential	Weibull	OS and PFS cross in the Nivo arm
Weibull	Weibull	OS and PFS cross in the Nivo arm
Gamma	Weibull	OS and PFS cross in the Nivo arm
Gompertz	Weibull	OS less than all cause
Log Logistic	Weibull	OS less than all cause

OS	PFS	Notes
Spline 1 knot odds	Weibull	OS less than all cause
Spline 2 knot odds	Weibull	OS less than all cause
Exponential	Gamma	OS and PFS cross in the first two weeks in the Docetaxel arm
Gompertz	Gamma	OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Log Logistic	Gamma	OS less than all cause
Spline 1 knot odds	Gamma	OS less than all cause
Spline 2 knot odds	Gamma	OS less than all cause
Exponential	Lognormal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Lognormal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Lognormal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gompertz	Lognormal	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Lognormal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Lognormal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2 knot hazard	Lognormal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1 knot odds	Lognormal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Lognormal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Lognormal	OS and PFS cross in the first week in the Docetaxel arm
Spline 2 knot normal	Lognormal	OS and PFS cross in the first week in the Docetaxel arm
Generalized gamma	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Exponential	Gompertz	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Gompertz	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause

OS	PFS	Notes
Gamma	Gompertz	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Gompertz	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Log Logistic	Gompertz	OS less than all cause
Spline 1 knot hazard	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Spline 2 knot hazard	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Spline 1 knot odds	Gompertz	OS less than all cause
Spline 2 knot odds	Gompertz	OS less than all cause
Spline 1 knot normal	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Spline 2 knot normal	Gompertz	OS and PFS cross in the Nivo arm OS less than all cause
Generalized gamma	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Exponential	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gamma	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Log Logistic	OS less than all cause
Gompertz	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Log Logistic	OS less than all cause
Spline 1 knot hazard	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot hazard	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	Notes
		OS less than all cause
Spline 1 knot odds	Log Logistic	OS less than all cause
Spline 2 knot odds	Log Logistic	OS less than all cause
Spline 1 knot normal	Log Logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Log Logistic	OS less than all cause
Generalized gamma	Spline 1 knot hazard	OS and PFS cross in the Nivo arm
Exponential	Spline 1 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 1 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 1 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Lognormal	Spline 1 knot hazard	OS and PFS cross in the Nivo arm
Gompertz	Spline 1 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 1 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Spline 1 knot hazard	OS and PFS cross in the Nivo arm
Spline 2 knot hazard	Spline 1 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1 knot odds	Spline 1 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Spline 1 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 1 knot hazard	OS and PFS cross in the Nivo arm
Spline 2 knot normal	Spline 1 knot hazard	OS and PFS cross in the Nivo arm
Generalized gamma	Spline 2 knot hazard	OS and PFS cross in the Nivo arm
Exponential	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	Notes
Gamma	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Lognormal	Spline 2 knot hazard	OS and PFS cross in the Nivo arm
Gompertz	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 2 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2 knot hazard	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1 knot odds	Spline 2 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Spline 2 knot hazard	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 2 knot hazard	OS and PFS cross in the Nivo arm
Spline 2 knot normal	Spline 2 knot hazard	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Generalized gamma	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Exponential	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gamma	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gompertz	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS less than all cause

OS	PFS	Notes
Spline 1 knot hazard	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot hazard	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 1 knot odds	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Spline 1 knot odds	OS and PFS cross in the Nivo arm OS less than all cause
Generalized gamma	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Exponential	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gamma	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS less than all cause
Gompertz	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause

OS	PFS	Notes
Spline 2 knot hazard	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 1 knot odds	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Spline 2 knot odds	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Generalized gamma	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Exponential	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gamma	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS less than all cause
Gompertz	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 1 knot normal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot hazard	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause

OS	PFS	Notes
Spline 1 knot odds	Spline 1 knot normal	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Spline 2 knot odds	Spline 1 knot normal	OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Spline 1 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Generalized gamma	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Exponential	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Weibull	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Gamma	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Lognormal	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS less than all cause
Gompertz	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Log Logistic	Spline 2 knot normal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot hazard	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm OS less than all cause
Spline 2 knot hazard	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot odds	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause

OS	PFS	Notes
Spline 2 knot odds	Spline 2 knot normal	OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 1 knot normal	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause
Spline 2 knot normal	Spline 2 knot normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm OS less than all cause

NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival.

Note: Only independent curves are included in the scenarios run. Additionally, the same PFS curves have been assumed for Nivolumab and Docetaxel.

Table C-2. Invalid Extrapolations for Non-Squamous NSCLC

OS	PFS	TTD	Notes
Generalised gamma	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Exponential	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Generalised gamma		OS less than all cause OS and PFS cross in the first week in the Nivo arm
Gompertz	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Generalised gamma		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot hazards	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot hazards	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot odds	Generalised gamma		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 1-knot normal	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot normal	Generalised gamma		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Gompertz	Exponential		OS less than all cause
Log-logistic	Exponential		OS less than all cause
Spline 1-knot odds	Exponential		OS less than all cause
Gompertz	Weibull		OS less than all cause
Log-logistic	Weibull		OS less than all cause
Spline 1-knot odds	Weibull		OS less than all cause
Exponential	Gamma		OS and PFS cross in the Docetaxel arm
Weibull	Gamma		OS and PFS cross in the first week in the Docetaxel arm
Gompertz	Gamma		OS less than all cause OS and PFS cross in the Docetaxel arm
Log-logistic	Gamma		OS less than all cause
Spline 1-knot odds	Gamma		OS less than all cause
Generalised gamma	Log-normal		OS and PFS cross in the first week in the Docetaxel arm
Exponential	Log-normal		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Log-normal		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Log-normal		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gompertz	Log-normal		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Log-normal		OS less than all cause OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot hazards	Log-normal		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 2-knot hazards	Log-normal		OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot odds	Log-normal		OS less than all cause OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds	Log-normal		OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot normal	Log-normal		OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot normal	Log-normal		OS and PFS cross in the first week in the Docetaxel arm
Generalised gamma	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Exponential	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Weibull	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Gamma	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Log-normal	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Gompertz	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Log-logistic	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot hazards	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot odds	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal	Gompertz		OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma	Log-logistic		OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Exponential	Log-logistic		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Log-logistic		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Log-logistic		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gompertz	Log-logistic		OS less than all cause OS and PFS cross in the Docetaxel arm
Log-logistic	Log-logistic		OS less than all cause
Spline 1-knot hazards	Log-logistic		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards	Log-logistic		OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 1-knot odds	Log-logistic		OS less than all cause
Spline 2-knot normal	Log-logistic		OS and PFS cross in the Nivo arm
Generalised gamma	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Exponential	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Gamma	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Log-normal	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Gompertz	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot hazards	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm

OS	PFS	TTD	Notes
Spline 1-knot odds	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot odds	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal	Spline 1-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Exponential	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm
Gompertz	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot hazards	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot hazards	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 1-knot odds	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot normal	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot normal	Spline 2-knot hazards		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Generalised gamma	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Exponential	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Gompertz	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot hazards	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 1-knot odds	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot odds	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal	Spline 1-knot odds		OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Exponential	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Gompertz	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot hazards	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot odds	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 2-knot odds	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot normal	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot normal	Spline 2-knot odds		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Generalised gamma	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Exponential	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm
Gompertz	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 1-knot normal		OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot hazards	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot hazards	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 1-knot odds	Spline 1-knot normal		OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot normal	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot normal	Spline 1-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Generalised gamma	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Exponential	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Gompertz	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic	Spline 2-knot normal		OS less than all causeOS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm

OS	PFS	TTD	Notes
Spline 1-knot hazards	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot hazards	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot odds	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 1-knot normal	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot normal	Spline 2-knot normal		OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Generalised gamma		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Gamma		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Log-normal		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Log-logistic		Generalised gamma	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 1-knot hazards		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Generalised gamma	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Generalised gamma	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Exponential	OS less than all cause
Log-logistic		Exponential	OS less than all cause
Spline 1-knot odds		Exponential	OS less than all cause
Exponential		Weibull	OS and PFS cross in the first week in the Docetaxel arm
Gompertz		Weibull	OS less than all cause OS and PFS cross in the first week in the Docetaxel arm
Log-logistic		Weibull	OS less than all cause
Spline 1-knot odds		Weibull	OS less than all cause
Exponential		Gamma	OS and PFS cross in the Docetaxel arm
Weibull		Gamma	OS and PFS cross in the first week in the Docetaxel arm
Gompertz		Gamma	OS less than all cause OS and PFS cross in the first two weeks in the Docetaxel arm
Log-logistic		Gamma	OS less than all cause
Spline 1-knot odds		Gamma	OS less than all cause
Generalised gamma		Log-normal	OS and PFS cross in the first week in the Docetaxel arm
Exponential		Log-normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Weibull		Log-normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Log-normal	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gompertz		Log-normal	OS less than all cause OS and PFS cross in the first week in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Log-normal	OS less than all cause OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot hazards		Log-normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot hazards		Log-normal	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot odds		Log-normal	OS less than all cause OS and PFS cross in the first two weeks in the Docetaxel arm
Spline 2-knot odds		Log-normal	OS and PFS cross in the first week in the Docetaxel arm
Spline 1-knot normal		Log-normal	OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot normal		Log-normal	OS and PFS cross in the first week in the Docetaxel arm
Generalised gamma		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Weibull		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Gamma		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Log-normal		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Log-logistic		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot hazards		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm

OS	PFS	TTD	Notes
Spline 2-knot hazards		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot odds		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Gompertz	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Log-logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Log-logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Log-logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gompertz		Log-logistic	OS less than all cause OS and PFS cross in the Docetaxel arm
Log-logistic		Log-logistic	OS less than all cause
Spline 1-knot hazards		Log-logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards		Log-logistic	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 1-knot odds		Log-logistic	OS less than all cause OS and PFS cross in the first week in the Docetaxel arm
Spline 2-knot normal		Log-logistic	OS and PFS cross in the Nivo arm
Generalised gamma		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Gamma		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm

OS	PFS	TTD	Notes
Log-normal		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the first week in the Nivo arm
Spline 1-knot hazards		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the first week in the Nivo arm
Spline 2-knot odds		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Spline 1-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma		Spline 2-knot hazards	OS and PFS cross in the Nivo arm
Exponential		Spline 2-knot hazards	OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Spline 2-knot hazards	OS and PFS cross in the Nivo arm OS and PFS cross in the first two weeks in the Docetaxel arm
Gamma		Spline 2-knot hazards	OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Log-normal		Spline 2-knot hazards	OS and PFS cross in the first week in the Nivo arm
Gompertz		Spline 2-knot hazards	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 2-knot hazards	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 1-knot hazards		Spline 2-knot hazards	OS and PFS cross in the Nivo arm

OS	PFS	TTD	Notes
Spline 2-knot hazards		Spline 2-knot hazards	OS and PFS cross in the Nivo arm
Spline 1-knot odds		Spline 2-knot hazards	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Spline 2-knot hazards	OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 2-knot hazards	OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot normal		Spline 2-knot hazards	OS and PFS cross in the Nivo arm
Generalised gamma		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot hazards		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 1-knot odds		Spline 1-knot odds	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm

OS	PFS	TTD	Notes
Spline 2-knot normal		Spline 1-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-normal		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 2-knot odds	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 1-knot hazards		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Spline 2-knot hazards		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Spline 2-knot odds	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Spline 2-knot odds	OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm

OS	PFS	TTD	Notes
Weibull		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Log-normal		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Gompertz		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 1-knot normal	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 1-knot hazards		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Spline 1-knot normal	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Spline 1-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Generalised gamma		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Exponential		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Weibull		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Gamma		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the first week in the Docetaxel arm
Log-normal		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm

OS	PFS	TTD	Notes
Gompertz		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm OS and PFS cross in the Docetaxel arm
Log-logistic		Spline 2-knot normal	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 1-knot hazards		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot hazards		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot odds		Spline 2-knot normal	OS less than all cause OS and PFS cross in the first two weeks in the Nivo arm
Spline 2-knot odds		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 1-knot normal		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm
Spline 2-knot normal		Spline 2-knot normal	OS less than all cause OS and PFS cross in the Nivo arm

NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

Note: The same OS and PFS curves have been assumed for OS and PFS.

Decision Support Unit Project Specification Form	
Project Numbers	ID900 nivolumab for treating non-squamous NSCLC
Appraisal titles	Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (ID900)
Synopsis of the technical issue	In the ACD2 document (ID900 non-squamous NSCLC), the committee recommended nivolumab within the CDF for the PD-L1 (>10%) subgroup, based on there being plausible potential for nivolumab to be cost-effective in adults with a PD-L1 expression of at least 10%. The ACD2 ICERs for the overall population only: - Above £80,000 for nivolumab compared with the main comparator of docetaxel; above £150,000 per QALY for nivolumab compared with nintedanib plus docetaxel in the non-squamous population (ID900 non-squamous NSCLC) <u>Method for extrapolation of OS</u>: a. The committee preferred the exponential extrapolation OS curve-fit b. The company preferred; based on evidence from the single arm CheckMate-003 study i. log-normal model for the non-squamous indication (section 4.10 of ACD2 for ID900 non-squamous NSCLC) c. The company ACD2 response proposes new analyses including an 'intermediary' assumption for long-term OS extrapolation in the overall population.

	2 year stopping rule: a. The company proposed a 2 year stopping rule at the last committee meeting. b. The committee did not believe that this was feasible. It concluded that it was uncertain how a stopping rule would be applied in clinical practice – see section 4.16 of ID900 for squamous NSCLC. c. The company ACD2 responses state that in the Checkmate-003 clinical trial an 1.8 years stopping rule was applied, in the ongoing Checkmate-153 they are investigating a 1 year stopping rule. Patient Access Scheme: The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nivolumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.
Questions to be answered:	1. Explore the goodness of fit for all OS extrapolation curves (company ACD2 response 'intermediary', committee-preferred ACD2 and company original, curves) relative to the clinical OS outcome data. 2. Explore rationales for a 2 year stopping rule and uncertainty of the long-term treatment effect 3. Propose a DSU-preferred OS curve-fit (chosen from the company ACD2 response 'intermediary', the committee-preferred ACD2 or company original curves), and reasons for the choice.

How will these questions be addressed?	1. Explore the goodness of fit and assess the OS outcomes for the different extrapolation curves relative to the clinical OS outcome data: a. company ACD2 response 'intermediary' curve b. committee-preferred ACD2 curve and c. company original curve 2. Present the DSU-preferred curve (with rationale) that best fits the clinical data available for nivolumab and its comparators for ID900 for non-squamous NSCLC from the curves: a. company ACD2 response 'intermediary' b. committee-preferred ACD2 c. company original 3. Present rationales for a 2 year stopping rule and what is the level of uncertainty associated with the long-term treatment effect.
DSU deliverables/outcomes	A report including analyses and responses to the above questions: 1. Explore the goodness of fit for all OS extrapolation curves (company ACD2 response 'intermediary', committee-preferred ACD2 and company original, curves) relative to the clinical OS outcome data. 2. Explore rationales for a 2 year stopping rule and uncertainty of the long-

	term treatment effect 3. Propose a DSU-preferred OS curve-fit (chosen from the company ACD2 response ‘intermediary’, the committee-preferred ACD2 or company original curves), and reasons for the choice.

31 March 2017

COMMENTS ON THE ONGOING APPRAISALS OF NIVOLUMAB FOR SQUAMOUS AND NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

22nd of February 2017

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk.

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Bermejo I. Comments on the ongoing appraisals of nivolumab for squamous and non-squamous non-small cell lung cancer. School of Health and Related Research (ScHARR), 2017.

Use of confidential data

Any 'commercial in confidence' data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any 'academic in confidence' data provided by the company, and specified as such, is highlighted in yellow and underlined in the review.

EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) asked the Decision Support Unit (DSU) to support the ongoing Single Technology Appraisals (STAs) on nivolumab for squamous non-small cell lung cancer (NSCLC) [ID811] and nivolumab for non-squamous NSCLC [ID900]. NICE asked the DSU to comment on the extrapolation methods for overall survival (OS) being considered: the committee-preferred approach, which comprised using the Kaplan-Meier (KM) curve up to a cut point and an exponential fitted to the rest of the data thereafter; the company-preferred approach, log-logistic and log-normal curves fitted to the full KM data of the pivotal trials for squamous and non-squamous NSCLC respectively; and, the company-proposed 'intermediary' approach, a generalised gamma fitted to the full KM data. NICE also asked the DSU to express its preference towards one of the approaches to describe the reasons for the choice.

After careful consideration of the evidence, the DSU believes that, especially based on the external evidence from CheckMate 003, the use of a slowly decreasing hazards function for the squamous NSCLC indication should be preferred over a long-term constant hazard extrapolation. The DSU prefers the 'intermediary' curve proposed by the company, a generalised gamma, as it features slowly decreasing hazards but without being as optimistic as the company-preferred log-logistic. However, the DSU acknowledges that linearity of the cumulative hazard cannot be rejected based on the available evidence and that the committee-preferred hybrid KM/exponential approach provides a good fit to the observed data and therefore considers that the committee-preferred approach provides a conservative extrapolation that is necessary to assess the considerable uncertainty on the OS extrapolation. On the other hand, the DSU believes that the evidence for the non-squamous indication is not supportive of the use of a decreasing hazards function. The DSU notes that it might not be clinically plausible to have different hazard progressions across indications, but that there is a significant difference in the available evidence. Therefore, after carefully reviewing the evidence, the DSU prefers to use the company's 'intermediary' curve to extrapolate OS in the squamous indication and the committee-preferred hybrid KM/exponential approach for the non-squamous indication.

NICE asked the DSU to explore the rationales for the two-year stopping rule for nivolumab. The company assumed in its base case that patients would stop treatment with nivolumab after two years but still keep the same benefit as those on treatment. The DSU notes that even if the

mechanism of action of nivolumab might be consistent with a sustained benefit after treatment discontinuation and even if the clinicians were willing to adhere to the stopping rule proposed by the company, there is no available evidence on the impact nivolumab discontinuation on patients' quality of life, progression free survival and overall survivall. In addition, the DSU notes that efficacy and cost estimates should come from a single source and that the stopping rule was not applied in the trials on which efficacy estimates were based (CheckMate 017 and CheckMate 057). Consequently, the DSU believes that the assumption that patients would enjoy the same benefit after treatment discontinuation is unreasonably optimistic and such an assumption should not be included in the base case analysis. However, it should be considered as a scenario analysis as part of the assessment of the uncertainty.

ABBREVIATIONS

AC	Appraisal committee
ACD	Appraisal consultation document
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BSC	Best supportive care
CS	Company submission
DSU	Decision Support Unit
ERG	Evidence Review Group
ICER	Incremental cost-effectiveness ratio
KM	Kaplan-Meier
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit Surveillance
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PPS	Post-progression survival
PSA	Probabilistic sens*itivity analysis
QALY	Quality-adjusted life years
RCC	Renal cell carcinoma
SEER	Surveillance, Epidemiology, and End Results Program
TSD	Technical Support Document

1. INTRODUCTION

The National Institute for Health and Care Excellence (NICE) asked the Decision Support Unit (DSU) to support the ongoing Single Technology Appraisals (STAs) on nivolumab for squamous non-small cell lung cancer (NSCLC) [ID811] and nivolumab for non-squamous NSCLC [ID900]. After the second appraisal consultation document (ACD2) of each appraisal had been published and the company had submitted new evidence in response to both ACD2s, NICE asked the DSU to:

1. Explore the goodness of fit for all overall survival (OS) extrapolation curves (company ACD2 response 'intermediary', committee-preferred ACD2 and company original, curves) relative to the clinical OS outcome data.
2. Propose a DSU-preferred OS curve-fit (chosen from the company ACD2 response 'intermediary', the committee-preferred ACD2 or company original curves), and reasons for the choice.
3. Explore rationales for a 2-year stopping rule and uncertainty of the long-term treatment effect.

The company's responses to the ACD2 of ID811 and ID900 included new evidence unrelated to the four tasks described above. However, it is outside of the remit of this report to critique this new evidence. Therefore, the DSU did not include in its base case the cost savings that the new PAS would result in other indications such as melanoma and renal cell carcinoma (RCC). Likewise, the DSU does not comment on the appropriateness of the different approaches to modelling PFS or the appropriateness of including nintedanib plus docetaxel as a comparator and applies the appraisal committee's (AC) preferences as expressed in the latest ACDs. Therefore, the DSU used the Evidence Review Group's (ERG) approach for extrapolating PFS for both squamous and non-squamous indications and included nintedanib plus docetaxel as a comparator in the non-squamous indication.

2. OVERALL SURVIVAL EXTRAPOLATION

2.1. SQUAMOUS NSCLC (ID811)

The original company submission (CS) included a comprehensive effort to extrapolate overall survival (OS), based on the guidance of the DSU TSD 14 on survival analysis [1]. The company tested that the proportional hazards assumption could not be rejected and fitted a wide range of

curves, but instead of fitting independent curves to each treatment arm, the company fitted a single model that used a coefficient to model the treatment effect between comparator and intervention. The company fitted both standard parametric models and flexible spline-based models, to the survival data from the pivotal trial CheckMate 017 [2]. The company restricted the number of knots in the splines to two, claiming that a higher number would over-fit the data. However, the DSU notes that the company did not provide a clinical justification for this restriction and that splines with a higher number of knots should also have been considered. The AC interpreted 2-knot splines as representing 3 heterogeneous subgroups of patients, each with a different survival profile [3]. The DSU notes that spline-based models represent a composed hazard function whose shape changes over time, rather than representing heterogeneous subgroups. The company then calculated measures of statistical fit of the curves fitted to the survival data using the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC). The company considered that the 2-knot hazard spline and the log-logistic model had the best statistical fit. The DSU notes that it is unclear how the company reached this conclusion, since the 2-knot hazard spline had neither the lowest AIC nor BIC and the sum of the AIC and BIC was lower for the log-normal function than for the 2-knot hazard spline. The company then compared the extrapolation using the log-logistic and the 2-knot hazard function against real-world data. Throughout the appraisal, the company has presented updated survival data from CheckMate 003, a long-term Phase I trial of patients with squamous and non-squamous NSCLC to support their selection of a function with a decreasing hazard. The company noted that the log-logistic function provided more accurate estimates based on the long-term survival (years 3 and 4) observed in CheckMate 003 (see Table 41 of the CS[4]). In order to validate their long-term extrapolation, the company also compared the estimates of the the 2-knot spline and the log logistic against National Lung Cancer Audit Surveillance (NLCA) and the Surveillance, Epidemiology, and End Results Program (SEER) data. The company noted that the log-logistic was more closely aligned with real-world conditional survival estimates and selected this model for use in its base case. The DSU notes that, given the substantial unexplained difference between the estimates of the two curves and the real-world data (they both considerably underestimated the conditional survival on docetaxel, see Table 42 of the CS), the log-logistic being more closely aligned to real-world evidence was of limited importance. The DSU notes that the log-logistic is an accelerated failure model and therefore the company's approach to fit a single model and to apply a hazard ratio (HR) as treatment effect is not appropriate.

In their response to the ACD2 [5], the company proposed a new approach to extrapolation OS termed the 'intermediary' curve, because it lies between the company's preferred curve (the log-logistic) and the committee-preferred approach explained below. The company specified that it was a generalised gamma and that it fulfilled the criteria that the predicted mortality was always greater than general mortality and that predicted OS was always higher than PFS. However, the company provided no additional information on the new curve's fit to the data and only provided a plot of the curve against a simplified KM curve.

The ERG noted that most of the survival gain (59%) of nivolumab versus docetaxel was attributable to the period after disease progression. Consequently, the ERG conducted a post-progression survival (PPS) analysis and noted that there was no statistically significant PPS gain in the nivolumab arm compared with the docetaxel arm (log-rank test, p=0.544). The committee concluded, based on the ERG's PPS analysis, that there was no sufficient evidence for a dramatic gain in survival after disease progression with nivolumab compared with docetaxel. However, the DSU notes that the ERG's PPS analysis is prone to selection bias and informative censoring. Selection bias may be present if the patients entering the post-progression state differ in their characteristics between trial arms. On the other hand, informative censoring may be present if patients with a better prognosis, due to entering the state later, are censored earlier in their time from progression to death. The DSU notes that selection bias could be addressed by adjusting for prognostic covariates at the time of progression and informative censoring could be addressed by using inverse probability weighting. Such an analysis can only be undertaken using individual patient data and information on the prognostic variables at baseline. The DSU believes that without addressing selection and informative bias, it is not clear whether the PPS analysis provides unbiased conclusions. The DSU notes that it is possible that the response status (whether a patient has responded or not) of those who have not yet progressed or died has an impact on overall survival. To illustrate this point further, a hypothetical propensity in some patients to benefit from treatment long-term would make a long-term flattening of the survival curve plausible. The clinical experts and the company argued that gain in survival after disease progression would be plausible and would be consistent with the mechanism of action of nivolumab.

The ERG applied its own approach to extrapolate OS based on Bagust and Beale[6]. Upon examination of the cumulative hazard plot, the ERG considered that long-term linear trends were established after 40 weeks in both trial arms. The ERG then estimated OS by applying the area under the curve (AUC) method using the trial data up to 40 weeks and using an

exponential curve fitted to the rest of the survival data thereafter. The ERG explains that the exponential curve was fitted from the final KM data point by successively adding additional data points and refitting the linear trend until the optimal fit was identified in terms of least-squares minimisation (R^2 maximisation). From the ERG's description, it is not clear whether the individual patient data were reproduced from the digitised KM using the method described by Guyot *et al.*[7] and if the number of patients at risk at each observation were taken into account in the least-squares minimisation, or if all data points in the curve were considered equally significant. The latter option would not take into account the fact that the observations at the end of the KM curve have a higher uncertainty. It is also not clear whether any non-linear functions fitted the data better. The ERG states that quadratic functions did not result in a significantly better fit, but statistical significance might not be as relevant in this case as other measures of statistical fit (such as the BIC, which penalises models with a higher number of parameters). The cut-point after which the exponential is used to extrapolate OS was defined by the optimum linear fit to the data points in the KM tail using least-squares minimisation. A recent study reported by Davies *et al.*[8] show that Bagust and Beale[6]'s approach can be very sensitive to the cut-point chosen. However, the impact of using different cut-points was not explored in the ERG's report. The clinical explanation provided by the ERG for long-term steady hazard rates happening only after 40 weeks in the trial was that patients with lower risk eventually dominate the population as the patients with high-risk die. However, the DSU notes that: if there are subgroups with different risks within the population, mixture models should be used; that no clinical explanation was provided as to why patients would be divided into two clearly separated risk groups and that the risk distribution is more likely to be a continuum across the population; that even if there were two separate groups with different constant risks, the overall risk would not be linear until the last one of the patients in the high-risk group died or was censored, which is unlikely to happen within the trial period unless the difference between the two risks is very high; and, that there is not enough evidence to assume that the risks for these two hypothetical subgroups to be constant. The ERG refers to the principle of parsimony to assume constant hazards unless such an assumption can be statistically rejected. The DSU notes that in order to provide a (in this case) conservative estimation, such an insight is valuable. However, in order to estimate the extrapolation that is most likely to be accurate, the model that best describes the available evidence and that has a better clinical plausibility should be preferred.

The DSU notes that the extrapolation of the hybrid KM/exponential approach is only based on a subset of the survival data, which might introduce bias and uncertainty in the extrapolation. The ERG argues that if all the survival data is used, the short survival experience of high-risk patients would dominate the estimation of future survival. However, the DSU notes that early survival data provides a valuable insight on how the hazard evolves over time, and that when using a hybrid KM/exponential extrapolation approach, the hazard of patients with a medium-risk could dominate the estimation of low-risk patients' survival. The ERG also notes the difficulty of fitting fully parametric models that accurately represent the early survival and still provide a plausible extrapolation of the unobserved long-term survival. The DSU acknowledges such a difficulty, but prefers fully parametric approaches that use all the available evidence, unless adequately justified by exceptional circumstances, and notes that alternatives to standard parametric models exist, such as flexible parametric models.

The ERG noted that the evidence from CheckMate 003, being single arm, did not contest the conclusion of their PPS analysis, namely that there is no statistically significant gain in PPS for nivolumab compared with docetaxel. In addition, the ERG also noted that their extrapolation of survival fell within the confidence interval of the KM curve from CheckMate 003 as provided in the company's response to the first ACD.

The committee concluded that the hybrid KM/exponential approach was more appropriate for extrapolating OS. The committee noted that the company-preferred log-logistic features an ever-decreasing hazard, which eventually falls below that of general mortality. Following the publication of the first ACD, the company added a cap so that the mortality hazard would not drop below that of the general population. However, the committee considered that the need for a cap implied that the log-logistic curve might be unsuitable for modelling OS in this case. The DSU notes that the committee-preferred approach uses a constant hazard and therefore fails to reflect the increasing mortality hazards with advancing age. The ERG argues that the age profile of surviving patients might be modified over time, countering the naturally expected increase in mortality. The DSU notes that when fitting curves to overall survival in advanced cancer trials, it is unlikely that the curve produced will capture the trend of general mortality hazard in the longer term. This is because mortality from cancer is orders of magnitudes higher than that of general mortality during the trial period and because trials are not long enough to capture the increase in general mortality. In such cases, the mortality observed in the trial could be the attributed solely to cancer after adjusting for the general mortality in the trial population. Consequently, general mortality could be included in the model separately. This way, curves

with ever decreasing hazards can be appropriately used to model cancer mortality if evidence to support decreasing hazards exists. However, the DSU agrees with the committee that evidence from CheckMate 017 is not conclusive to support the company's approach. However, considerable uncertainty remains as to whether the hybrid KM/exponential extrapolation is more accurate than the company-preferred log-logistic or 'intermediary' curves.

The committee considered that the evidence from the CheckMate 003 trial was not conclusive in supporting the company-preferred log-logistic curve over the hybrid KM/exponential extrapolation, as it considered that both extrapolations were consistent with longer-term survival results seen in the trial. In addition, it criticised the trial as being a limited source of corroboration as it adopted a single-arm design, it included people with either squamous or non-squamous NSCLC and included only a small population size at later time points. The DSU acknowledges that the CheckMate 003 population included patients of squamous and non-squamous indications but considers that the size of the population including squamous and non-squamous patients (129 patients) is similar to that of CheckMate 017 (135).

In their response to ACD2, the company provided updated OS data for CheckMate 003 and, upon request, separate KM curves for patients with squamous and non-squamous NSCLC. The DSU replicated the underlying individual patient data from KM curve for patients with squamous NSCLC using the method described by Guyot *et al.*[7] and plotted it against the three extrapolation methods being considered: the company's preferred (log-normal), the 'intermediary' curve (generalised gamma) and the hybrid KM/exponential. As shown in

Figure 1, the ERG's extrapolation of OS lies outside the confidence interval of the KM curve from CheckMate 003. However, the DSU advises caution in interpreting this result, as the confidence interval of the replicated KM curve is only an approximation.

Figure 1 also shows that the KM curve from CheckMate 017 (see the first part of the hybrid KM/exponential) is very similar to that of patients with squamous NSCLC in CheckMate 003.

Figure 1: KM of patients with squamous NSCLC in CheckMate 003 plotted against the different extrapolations of OS based on CheckMate 017

The DSU is aware of potential differences between the populations in CheckMate 017 and CheckMate 003 but notes that shapes of the KMs are very similar in both trials for the squamous population. The DSU acknowledges that the population of CheckMate 003 is relatively small, especially when only squamous patients are considered. However, the DSU considers that the evidence from CheckMate 003 supports the appropriateness of a curve with decreasing hazards.

The DSU believes that the existing evidence, especially the external evidence from CheckMate 003, supports the use of a function with decreasing hazards for nivolumab on squamous NSCLC. However, the DSU notes that the linearity of the long-term hazard cannot be rejected and that the hybrid KM/exponential extrapolation provides a good fit to the observed survival data. This implies that if the hazard is decreasing over time, it is decreasing at a very slow pace. Under such high uncertainty, the DSU has a slight preference towards the company-proposed 'intermediary' generalised gamma curve, as it reflects a slowly decreasing hazard, but without the optimistic extrapolation estimated by the long tail of the log-logistic. However, the DSU notes that the committee-preferred hybrid KM/exponential extrapolation approach is necessary to assess the considerable uncertainty on OS extrapolation.

2.2. NON-SQUAMOUS NSCLC (ID900)

In their original submission, the company followed a structured process following the DSU TSD for survival analysis to choose an OS extrapolation curve. In their original submission, the company expressed its preference towards a generalised gamma curve for extrapolation based on goodness-of-fit statistics, clinical plausibility, visual examination and external data validation. A key factor in choosing the generalised gamma was that, based on the mentioned criteria, it provided a good fit to both treatment arms (nivolumab and docetaxel). The DSU notes that the company's claim of immune-oncologics having a different hazard progression compared with chemotherapy may have justified using different functions for each arm, especially given that throughout the appraisal, the company has presented updated evidence on long-term survival from CheckMate 003 to support their selection of a function with a decreasing hazard.

After consultation, partly because of criticism from the committee and partly due to the availability of 24-month data, the company adopted a log-normal curve in their base case arguing that it had a better statistical fit than the generalised gamma. In their response to the ACD2 [9], the company have returned to a new generalised gamma, termed the 'intermediary' curve, as it provides a compromise between the optimistic extrapolation of the company-preferred log-normal and the committee-preferred hybrid KM/exponential approach. The company specified that it was the new curve fulfilled the criteria that the predicted mortality was always greater than general mortality and that predicted OS was always higher than PFS. However, the company provided no additional information on the new curve's fit to the data or how it calculated the new curve.

The ERG identified two subgroups, (i) patients who received post-progression treatment and (ii) patients who did not receive post-progression treatment, and fitted lines to the cumulative hazard plots of these subgroups starting at 8 and 12 months respectively. The ERG then applied a mixed exponential approach, consisting of applying different hazards to the different subgroups. The DSU notes that the ERG did not compare linear fits against non-linear ones and that the impact of the chosen cut-points was not assessed in sensitivity analyses. The ERG noted that its approach resulted in a very similar curve to the 2-knot spline explored by the company, which had the best statistical fit (AIC and BIC) for nivolumab. However, the curves in Figure 32 of the CS and Figure 20 in the ERG's report differ after 4.5 years. The ERG considered that the evidence from CheckMate 003 did not invalidate its original approach, because: (i) the ERG understood that the survival data from the Checkmate 003 trial could not

be used to validate the company's OS projections due to the differing survival profiles between the two trials (see Figure 2); and, (ii) the ERG claimed, based on fitting a line to a cumulative hazard plot, that mortality hazard was also linear in the CheckMate 003 trial after 15 months. The DSU notes that the linear fit was not compared against non-linear fits and that it is unclear why the hazard was assumed to be linear.

Figure 2: KM curves for nivolumab in CheckMate 003 and CheckMate 057 (replicated from Figure 17 in the ERG report)

The committee criticised the company's use of functions with an ever-decreasing mortality rate (generalised gamma and the log-normal), which the company considered to be supported by the cumulative hazard plots of single-arm CheckMate 003. The committee argued against curves with decreasing hazard-rates because it did not consider that the evidence was conclusive enough to support a decreasing hazard and because these curves reach a point whereby the mortality risk of patients on nivolumab is estimated to be lower than that of the general population. However, the DSU notes that the hybrid KM/exponential, which assumes a constant hazard of death, also fails to reflect the increasing mortality hazard with advanced age.

The company modelled OS for the comparison of nivolumab versus nintedanib plus docetaxel by applying a hazard ratio (based on survival data from LUME-Lung 1 trial [10]) to the comparator arm. The ERG noted that the proportional hazards assumption did not hold and noted that applying hazard ratios to an accelerated failure model such as the log-normal is not appropriate. Therefore, the ERG undertook its own approach, consisting of an unadjusted

indirect comparison in order estimate overall survival for nivolumab compared with nintedanib plus docetaxel. The committee noted that the unadjusted comparison had limitations but it concluded that the ERG's approach was more plausible than the company's. The committee considered that the same issues regarding the extrapolation of OS also affected this comparison and concluded that the ERG's approach was more appropriate.

The DSU agrees with the committee and the ERG in that the available evidence does not support the choice of a decreasing-hazard function as preferred method for OS extrapolation of patients with non-squamous NSCLC. The DSU agrees with the ERG that the differences between the KM curves from Checkmate 057 and CheckMate 003 as shown in Figure 2 suggest that the differences between these trials are significant. It is worth noting that the population of CheckMate 003 was divided into three dosing regimes: 1mg/kg, 3mg/kg (as in CheckMate 057) and 10 mg/kg. Gettinger *et al.*[11] show that the OS was significantly higher in patients with non-squamous NSCLC on 3mg/kg (median OS 18.2 months) compared with those on 1mg/kg (9.9 months) and 10 mg/kg (7.4 months). The DSU notes that the higher survival of the 3mg/kg subgroup could explain the higher survival observed in CheckMate 057 in the first two years. The difference in overall survival between the treatment groups would also explain the non-linear hazard observed in CheckMate 003 in the non-squamous population. Such a difference in survival was not observed amongst subgroups in the squamous population of CheckMate 003 (median OS of 9.2, 8.0, 10.5 months for 1mg/kg, 3mg/kg, 10mg/kg respectively)[11]. Therefore, the DSU concludes that the survival evidence from CheckMate 003 for the non-squamous population is highly confounded and cannot be directly applied to the decision problem.

In addition, the DSU considers that the company's extrapolation of OS for nintedanib plus docetaxel is inappropriate for the reasons stated by the company and the ERG. Consequently, considering its limitations noted by the company and the committee, the DSU prefers the committee-preferred hybrid KM/exponential to OS extrapolation for patients with non-squamous NSCLC. However, the DSU believes that the company's 'intermediary' curve should be used to assess the uncertainty around the ICER for nivolumab compared with docetaxel and nintedanib plus docetaxel.

3. DURATION OF TREATMENT

The company argues that given the mechanism of action of nivolumab, it is not appropriate to treat patients until disease progression, as is common with other cancer therapies. Therefore, the company proposed a 2-year stopping rule according to which patients would be on treatment for a maximum timespan of two years. The company noted that the Scottish Medicines Consortium (SMC) have recommended nivolumab in the treatment of squamous NSCLC under the condition that a 2-year stopping rule is applied.

The committee noted that the summary of product characteristics for nivolumab did not include a 2-year stopping rule. The committee therefore considered that it was unlikely that clinicians would apply such a stopping rule if they believed that the patient was still benefitting from the treatment. The committee concluded that it was uncertain of the application of a stopping rule in clinical practice and the assumption should not be applied to the economic modelling.

In addition, no stopping rule was applied in the pivotal clinical trials (CheckMate 017 for squamous and CheckMate 037 for non-squamous) used to estimate the efficacy of the drugs. The company noted that in the Checkmate 003 trial, a stopping rule of 96 weeks (1.8 years) was applied and that 6 out of 7 patients who had a response to treatment (complete or partial) maintained that response beyond 96 weeks. The DSU notes that the durability of this response is unclear and it is unclear whether patients who stopped treatment had the same benefit as those who continued treatment. The DSU notes that, as shown in

Figure 3, the hazard does not seem to increase after 1.8 years, which would suggest that patients in CheckMate 003 who stopped treatment after that time did not suffer an increased hazard after treatment discontinuation. However, remaining on treatment might have decreased the hazard even further and as discussed previously, it is unclear whether the hazard in CheckMate 003 is affected by the different dosage regimens and therefore whether it can be used to inform the decision problem.

Figure 3: Cumulative hazard plot of all patients on nivolumab in CheckMate 003

The company also noted that an ongoing study (Checkmate 153) is investigating a 1-year stopping rule; the initial results of this study are due to be published in 2017. The DSU notes that the results from CheckMate 153 could help reduce the uncertainty around the impact of the 2-year stopping rule on health gains. However, given the current uncertainty, the DSU believes that assuming that all patients will stop treatment after 2 years and that they will keep the same benefits as whilst on treatment in the base case is likely to be unreasonably optimistic.

In their responses to both ACD2s [5, 9], the company referred to a recent appraisal, "Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy"[12], where pembrolizumab was recommended with a 2-year stopping rule. The DSU notes that the company's base case assumed 25% of patients would continue on treatment after two years and that scenario analyses were presented where 100% remained on treatment after two years.

4. CONCLUSIONS

Overall survival

The evidence on OS for the squamous population is not conclusive to reject a long-term steady hazard but clinical plausibility and the external evidence from CheckMate 003 might justify a slight preference towards the use of a slowly decreasing hazards function for the squamous indication. The DSU considers that the 'intermediary' curve proposed by the company provides the most plausible extrapolation of the three considered, as it features a compromise between the company's preferred log-logistic and the hybrid KM/exponential approach featuring long-term constant hazards. However, the hybrid KM/exponential approach should be used in exploratory analyses to assess the considerable remaining uncertainty on the OS extrapolation.

On the other hand, the DSU considers that the available evidence for the non-squamous indication is not supportive of the use of a decreasing hazards function. The DSU notes that this apparent inconsistency might be a shortcoming of the available evidence and it might be clinically implausible to have different hazard progressions across indications. Therefore, the the DSU prefers the hybrid KM/mixed exponential for the base-case analysis for the non-squamous indication and recommends the use of the 'intermediary' curve to assess the uncertainty on OS extrapolation.

2-year stopping rule

The DSU notes that even if the mechanism of action of nivolumab might explain a sustained benefit after treatment discontinuation and even if the clinicians were willing to adhere to the stopping rule proposed by the company, there is no comparative evidence available of the effectiveness of nivolumab after treatment discontinuation. In addition, efficacy and cost estimate should come from a single source and the stopping rule was not applied in CheckMate 017 and CheckMate 057. Therefore, the DSU believes that assuming that patients will experience the same benefit after treatment discontinuation is unreasonably optimistic and such an assumption should not be included in the base case analysis. However, the assumption should be considered in a scenario analysis for a comprehensive assessment of the uncertainty.

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20th March 2017

Dear Sir / Madam,

Thank you for the opportunity to respond to the Decision Support Unit's (DSU) report for the ongoing single technology appraisal (STA) for nivolumab in previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900].

We welcome the comments that the DSU have provided, and given the body of evidence that was available to them at the time of review they are fair and accurate. We now have additional long term overall survival data from the key clinical trial (CheckMate 057) that manages much of the uncertainty associated with the long term benefit associated with nivolumab. Therefore the assumptions on which the requested analysis are run, should be updated in-line with this new data. For completeness and transparency the rest of the results are also presented

BMS is keen to continue working with NICE to find a mutually agreeable way forward that will allow nivolumab to be used in the patient group envisaged by the license in both England and Wales.

Kind Regards,

[redacted]

Health Economics and Outcomes Research

Bristol-Myers Squibb Company

Introduction

The last appraisal committee meeting (ACM) for ID900 was held on 10th August 2016. A negative ACD was subsequently published on October 14th 2016. Since this time a proposal has been shared with NICE where a number of pricing solutions were discussed, as well as the initial presentation of an intermediary OS curve (generalised gamma) which lay between the two approaches – BMS base case (log-logistic) and the ERG (exponential). The DSU were then asked to provide their opinion on this approach, and BMS welcome their comments, as well as the pragmatism NICE has shown in involving them.

We are pleased that the long term benefit of nivolumab has been acknowledged in the second ACD, as well as the DSU report. We also understand that there is uncertainty associated with the modelling of this benefit (which is an inherent part of any cost-effectiveness modelling), especially given the maturity of data that was available at the last ACM. [redacted]

Additional Data

The pivotal trial in this appraisal – CheckMate 057 is a phase III randomised controlled trial. At the time of the DSU review, only 2-year data were available. Since then, a survival sweep has been conducted which collected the proportion of patients that are still alive in this trial. The Kaplan-Meier curves are presented below, all the patients have been in the trial for a minimum of 3 years, see figure 1. Previously patients with advanced and metastatic relapsed non-squamous NSCLC were expected to have a median overall survival of 6 months with current standard of care.

This additional data from CheckMate 057 demonstrates the superiority of nivolumab over docetaxel in these patients, and [redacted] (Figure 1).

To further support this, 5-year overall survival data from the phase I clinical trial CheckMate 003 are also presented (Figure 2). Previously the committee had only seen 4-year data from this trial. Based on visual inspection, the shape of this curve is similar to that of the curve presented for CheckMate 057, and given that there is no clear clinical rationale as to why these should diverge, it can be assumed that they both support the log-logistic curve (BMS base case).

[redacted]

[redacted]

As can be seen from table 1, there is a similarity of data across studies that supports the approach of using CheckMate 003 OS results to validate the survival extrapolation in CheckMate 017 and 057, the log-logistic curve. Patient characteristics are similar across the 3 studies and do not clearly show a favourable population in one, versus the others.

The percentage of patients surviving at available milestones is very similar or better when compared to 003 across landmarks available to date. [redacted] as seen with immunotherapy treatment in lung and melanoma (Figure 1). Given that there is no clear clinical rationale as to why these should diverge, it can be assumed that they both support the log-logistic curve (BMS base case).

As shown in table 1, the data clearly shows a similar pattern with nivolumab across the studies. Nivolumab response rates are substantially higher than with docetaxel in the two phase 3 studies, and are within a narrow range (17.1 to 20%). In addition, the duration of response with nivolumab in each of the 3 studies was similar (17.0 to 25.4 months), and, consistent with the durability of benefit with immune-oncology in melanoma and now NSCLC, this duration was 3 to 4 times what was observed with docetaxel in CheckMate 017 and 057 (5.6 to 8.4 months).

Table 1: Summary of response rates, duration of response, and OS rates from CheckMate 003, 017, and 057

	Nivolumab	**Docetaxel**

CheckMate	003	017	057	017	057
Response					
ORR	17.1 %	20.0 %	19.2 %	8.8%	12.4%
Median DOR (months)	17.0 months	25.2 months	17.2 months	5.4 months	5.6 months
Overall Survival	**% (Number at risk)**				
6 months OS	65.9 (83)	63.7 (86)	66.4 (194)	50.4 (69)	67.9 (195)
12 months OS	41.8 (48)	42.2 (57)	50.7 (148)	24.1 (33)	39.3 (112)
18 months OS	31.2 (35)	28.1 (38)	39.2 (112)	12.4 (17)	23.5 (67)
24 months OS	24.8 (26)	23.0 (31)	28.7 (82))	8.0 (11)	16.1 (46)
36 months OS	18.4 (12)	[redacted]	[redacted]	5.8 (8)	9.4 (26)
48 months OS	[redacted]	NA	NA		
60 months OS	[redacted]	NA	NA		

Pertinence of additional data to the decision problem

The 3-year OS data from CheckMate 057 and 5 year OS data from CheckMate 003 confirm that the extrapolation as originally submitted by BMS (log-logistic) is valid, and in fact underestimates the benefit nivolumab brings patients, see table 2, figures 3 and 4. Therefore the log-logistic extrapolation should be considered as the base case for decision making.

As requested by NICE, results with the intermediary curve (generalised gamma) are also provided, but we urge the committee, in light of this additional long term data to consider this as a worst case scenario.

We agree with the DSU that a function that takes into account a decreasing hazard should be used to assess long term benefit of nivolumab in squamous NSCLC. Further to this, we believe this to also be the case in non-squamous NSCLC, and that a log-logistic curve should be used, and this is further supported by the additional data now available.

In addition, a clinical consensus statement has been written and signed where a number of practicing oncologists confirmed that it would be inappropriate to assume that patients on an immuno-therapy should be considered to have a constant mortality rate.

A similar long term effect, has been observed in other tumours - most notably nivolumab for melanoma and renal cell carcinoma (RCC), both of which have been appraised and recommended for use by NICE. This has also been seen in another immuno-therapy, ipilimumab in melanoma.

The survival rates from CheckMate 057 and CheckMate 003, as well as the proportion of patients alive in the models (dependant on which extrapolation used) is presented in table 2.

Table 2: Survival rates from the clinical trials and estimates from the three modelling approaches

Data Source	Curve	Proportion Alive						
		1 year	2 years	3 years	4 years	5 years	10 years	15 years
Non-Squamous								
CheckMate 057		51%	29%	[redacted]	[redacted]			
CheckMate 003		42%	24%	18%	[redacted]	[redacted]		
Model estimates for nivolumab OS	BMS Log-logistic	46.78%	27.78%	18.75%	13.61%	10.35%	3.83%	1.93%
	Intermediary Generalised gamma	47.64%	27.35%	17.58%	12.08%	8.70%	2.47%	0.98%
	ERG Exponential	51.61%	26.63%	13.74%	7.09%	3.66%	0.13%	0.00%

*based on limited censored observations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Methods

Patients in CheckMate 057 were treated as long as clinical benefit was observed or until treatment was no longer tolerated by the patient. Based on the mode of action of nivolumab BMS has proposed to NICE that it would be used for a maximum of 2 years at which point treatment would be stopped. This approach was accepted in the recent pembrolizumab appraisal for NSCLC which has a similar mode of action [TA 428].

The committee raised concerns that the clinical benefit of nivolumab might be expected to decline at 2 years when the maximum treatment duration has been reached – a treatment waning effect. CheckMate 003 had a treatment stopping rule at 96-weeks and argues against treatment waning post stopping. In CheckMate 003, 14 out of 16 patients were still alive at 5 years, they remained off any therapy and have maintained their response.

As can be seen in table 2, there is a decrease in OS in CheckMate 003 of 7% from 2 years to 3 years and then a subsequent decrease of [redacted]%. Looking at the BMS base case there is already a decrease in the OS from 2 years to 3 years of 9.03%. Then there is a further decrease of 5.14% at 4 years.

BMS therefore argues that a treatment waning effect has already been taken into account in the BMS base-case and there is no need to add in an additional decrease in OS after 2 years.

In the intermediary curve there is a larger decrease of 9.77% at 3 years already included which BMS views as a worst case scenario.

Despite this, BMS have been requested to consider 3 treatment waning scenarios where the treatment effect is reduced at 3, 5, and 10 years. These results are

presented below. It should be noted however that the reduction at 3, 5 and 10 years should not be considered if a 2 year stopping rule is not implemented because the patient is still on treatment, the results of this are provided but greyed out.

One of the scenarios that NICE wishes to explore is the impact of varying the number of patients that remain on treatment after 2 years. This is despite our confidence that the NHS will have the appropriate systems to control this as discussed in the ACD of pembrolizumab for NSCLC [ID 840].

BMS is confident that at 2 years patients will stop therapy, however we have provided a scenario below which reflects the proportion of patients remaining on treatment after 2 years in CheckMate 057 - 9%.

Results

As requested by NICE, the following tables have been populated with results that reflect the assumptions presented in table 3. It should be noted however that given the new data that is now available, we present three sets of results – the BMS base case and the intermediary worst case, and also the ERG case, as requested by NICE. The PFS extrapolation requested is not the assumption which BMS preferred but we have provided this analysis as requested.

Table 3: Comparison of the assumptions used to populate the results tables below

	Table 4: BMS Base case	**Table 5: Intermediary worst case**	**Table 6: ERG case**
Utility values	PFS: 0.713 PD: 0.5685	PFS: 0.713 PD: 0.5685	PFS: 0.713 PD: 0.5685
PFS Extrapolation	Exponential	Exponential	Exponential
OS Extrapolation	Log-logistic	Generalised gamma	Exponential
PAS	[redacted]	[redacted]	[redacted]
Melanoma / RCC Credit	Not included	Not included	Not included

Table 4: Base case results as requested by NICE (BMS Log-logistic)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £26,012 Inc. QALYs: 0.46 ICER: £57,081 Probabilistic ICER: £57,204	Inc. Costs: £25,842 Inc. QALYs: 0.45 ICER: £58,027 Probabilistic ICER: £58,026	Inc. Costs: £25,262 Inc. QALYs: 0.41 ICER: £61,371 Probabilistic ICER: £61,418	Inc. Costs: £24,686 Inc. QALYs: 0.38 ICER: £65,097 Probabilistic ICER: £65,021
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £24,957 Inc. QALYs: 0.46 ICER: £54,764 Probabilistic ICER: £54,731	Inc. Costs: £24,786 Inc. QALYs: 0.45 ICER: £55,656 Probabilistic ICER: £55,443	Inc. Costs: £24,207 Inc. QALYs: 0.41 ICER: £58,809 Probabilistic ICER: £58,693	Inc. Costs: £23,643 Inc. QALYs: 0.38 ICER: £62,349 Probabilistic ICER: £62,535
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £24,731 Inc. QALYs: 0.46 ICER: £54,270 Probabilistic ICER: £54,195	Inc. Costs: £24,561 Inc. QALYs: 0.45 ICER: £55,151 Probabilistic ICER: £55,439	Inc. Costs: £23,982 Inc. QALYs: 0.41 ICER: £58,262 Probabilistic ICER: £58,229	Inc. Costs: £23,421 Inc. QALYs: 0.38 ICER: £61,762 Probabilistic ICER: £62,252
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £24,605 Inc. QALYs: 0.46 ICER: £53,992 Probabilistic ICER: £53,793	Inc. Costs: £24,435 Inc. QALYs: 0.45 ICER: £54,866 Probabilistic ICER: £54,929	Inc. Costs: £23,855 Inc. QALYs: 0.41 ICER: £57,954 Probabilistic ICER: £58,107	Inc. Costs: £23,296 Inc. QALYs: 0.38 ICER: £61,432 Probabilistic ICER: £61,457

Table 5: Worst case as requested by NICE (Intermediary – Generalised gamma)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £25,464 Inc. QALYs: 0.42 ICER: £60,135 Probabilistic ICER: £60,145	Inc. Costs: £25,314 Inc. QALYs: 0.41 ICER: £61,080 Probabilistic ICER: £61,998	Inc. Costs: £24,802 Inc. QALYs: 0.38 ICER: £64,451 Probabilistic ICER: £66,097	Inc. Costs: £24,267 Inc. QALYs: 0.35 ICER: £68,385 Probabilistic ICER: £71,438
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £24,408 Inc. QALYs: 0.42 ICER: £57,643 Probabilistic ICER: £58,206	Inc. Costs: £24,259 Inc. QALYs: 0.41 ICER: £58,533 Probabilistic ICER: £60,141	Inc. Costs: £23,747 Inc. QALYs: 0.38 ICER: £61,710 Probabilistic ICER: £63,596	Inc. Costs: £23,224 Inc. QALYs: 0.35 ICER: £65,448 Probabilistic ICER: £67,939
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £24,183 Inc. QALYs: 0.42 ICER: £57,111 Probabilistic ICER: £58,244	Inc. Costs: £24,034 Inc. QALYs: 0.41 ICER: £57,989 Probabilistic ICER: £58,813	Inc. Costs: £23,522 Inc. QALYs: 0.38 ICER: £61,125 Probabilistic ICER: £62,818	Inc. Costs: £23,002 Inc. QALYs: 0.35 ICER: £64,821 Probabilistic ICER: £67,962
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £24,056 Inc. QALYs: 0.42 ICER: £56,812 Probabilistic ICER: £57,421	Inc. Costs: £23,907 Inc. QALYs: 0.41 ICER: £57,684 Probabilistic ICER: £58,219	Inc. Costs: £23,395 Inc. QALYs: 0.38 ICER: £60,796 Probabilistic ICER: £61,455	Inc. Costs: £22,877 Inc. QALYs: 0.35 ICER: £64,469 Probabilistic ICER: £67,210

Table 6: ERG curve results as requested by NICE (Exponential)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £23,187 Inc. QALYs: 0.29 ICER: £79,813 Probabilistic ICER: £79,643	Inc. Costs: £23,187 Inc. QALYs: 0.29 ICER: £79,823 Probabilistic ICER: £80,006	Inc. Costs: £23,162 Inc. QALYs: 0.29 ICER: £80,120 Probabilistic ICER: £80,193	Inc. Costs: £23,070 Inc. QALYs: 0.28 ICER: £81,018 Probabilistic ICER: £81,155
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £22,132 Inc. QALYs: 0.29 ICER: £76,180 Probabilistic ICER: £76,152	Inc. Costs: £22,131 Inc. QALYs: 0.29 ICER: £76,189 Probabilistic ICER: £76,586	Inc. Costs: £22,107 Inc. QALYs: 0.29 ICER: £76,471 Probabilistic ICER: £76,511	Inc. Costs: £22,027 Inc. QALYs: 0.28 ICER: £77,357 Probabilistic ICER: £77,715
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £21,907 Inc. QALYs: 0.29 ICER: £75,405 Probabilistic ICER: £75,679	Inc. Costs: £21,906 Inc. QALYs: 0.29 ICER: £75,413 Probabilistic ICER: £75,469	Inc. Costs: £21,882 Inc. QALYs: 0.29 ICER: £75,693 Probabilistic ICER: £75,681	Inc. Costs: £21,805 Inc. QALYs: 0.28 ICER: £76,577 Probabilistic ICER: £76,879
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £21,780 Inc. QALYs: 0.29 ICER: £74,969 Probabilistic ICER: £75,294	Inc. Costs: £21,779 Inc. QALYs: 0.29 ICER: £74,977 Probabilistic ICER: £75,082	Inc. Costs: £21,755 Inc. QALYs: 0.29 ICER: £75,255 Probabilistic ICER: £75,407	Inc. Costs: £21,680 Inc. QALYs: 0.28 ICER: £76,137 Probabilistic ICER: £76,239

Simple PAS – RCC / Melanoma Credit

At the nivolumab ACM in August 2016, the committee discussed whether the impact of wider benefit to the NHS could be taken into account because the simple discount agreed to would apply across all indications. This approach also was acknowledged in the recent appraisal of pembrolizumab for NSCLC and included in Section 4.18 of the FAD (TA428), which states:

"[the committee] was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications."

With this argument both nivolumab for melanoma and RCC would be available with a [redacted]% discount, resulting in a lower treatment costs for these indications. To account for these savings, the melanoma and RCC cost-effectiveness models were run at the cost-effective PAS levels ([redacted]% and [redacted]%, respectively) and then again at [redacted]%. The difference in cost per melanoma or RCC patient treated with nivolumab then was weighted for size of patient population and subtracted from the incremental costs in the models used to derive the incremental cost-effectiveness ratios (ICERs) for the NSCLC indications of nivolumab.

BMS have presented scenarios (Table 7, 8 and 9) where a credit from melanoma and RCC is applied (given that the PAS will apply across all licensed indications of nivolumab).

Table 7: Base case results as requested by NICE (BMS log-logistic including credit)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £23,630 Inc. QALYs: 0.46 ICER: £51,854 Probabilistic ICER: £51,963	Inc. Costs: £23,460 Inc. QALYs: 0.45 ICER: £52,678 Probabilistic ICER: £52,672	Inc. Costs: £22,880 Inc. QALYs: 0.41 ICER: £55,584 Probabilistic ICER: £55,797	Inc. Costs: £22,304 Inc. QALYs: 0.38 ICER: £58,816 Probabilistic ICER: £59,129
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £22,575 Inc. QALYs: 0.46 ICER: £49,537 Probabilistic ICER: £49,665	Inc. Costs: £22,404 Inc. QALYs: 0.45 ICER: £50,308 Probabilistic ICER: £50,248	Inc. Costs: £21,825 Inc. QALYs: 0.41 ICER: £53,022 Probabilistic ICER: £52,997	Inc. Costs: £21,261 Inc. QALYs: 0.38 ICER: £56,067 Probabilistic ICER: £55,703
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £22,349 Inc. QALYs: 0.46 ICER: £49,043 Probabilistic ICER: £49,055	Inc. Costs: £22,179 Inc. QALYs: 0.45 ICER: £49,802 Probabilistic ICER: £50,014	Inc. Costs: £21,600 Inc. QALYs: 0.41 ICER: £52,475 Probabilistic ICER: £52,632	Inc. Costs: £21,039 Inc. QALYs: 0.38 ICER: £55,481 Probabilistic ICER: £55,573
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £22,223 Inc. QALYs: 0.46 ICER: £48,765 Probabilistic ICER: £49,071	Inc. Costs: £22,052 Inc. QALYs: 0.45 ICER: £49,518 Probabilistic ICER: £49,711	Inc. Costs: £21,473 Inc. QALYs: 0.41 ICER: £52,167 Probabilistic ICER: £52,106	Inc. Costs: £20,914 Inc. QALYs: 0.38 ICER: £55,151 Probabilistic ICER: £55,161

Table 8: Intermediary results (worst-case scenario) as requested by NICE (generalised gamma including credit)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £23,082 Inc. QALYs: 0.42 ICER: £54,510 Probabilistic ICER: £52,988	Inc. Costs: £22,932 Inc. QALYs: 0.41 ICER: £55,332 Probabilistic ICER: £54,512	Inc. Costs: £22,420 Inc. QALYs: 0.38 ICER: £58,261 Probabilistic ICER: £57,108	Inc. Costs: £21,885 Inc. QALYs: 0.35 ICER: £61,672
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £22,026 Inc. QALYs: 0.42 ICER: £52,017 Probabilistic ICER: £50,799	Inc. Costs: £21,877 Inc. QALYs: 0.41 ICER: £52,785 Probabilistic ICER: £52,331	Inc. Costs: £21,365 Inc. QALYs: 0.38 ICER: £55,520 Probabilistic ICER: £55,427	Inc. Costs: £20,842 Inc. QALYs: 0.35 ICER: £58,735 Probabilistic ICER: £57,896
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £21,801 Inc. QALYs: 0.42 ICER: £51,485 Probabilistic ICER: £50,667	Inc. Costs: £21,652 Inc. QALYs: 0.41 ICER: £52,242 Probabilistic ICER: £51,313	Inc. Costs: £21,140 Inc. QALYs: 0.38 ICER: £54,935 Probabilistic ICER: £55,007	Inc. Costs: £20,620 Inc. QALYs: 0.35 ICER: £58,108 Probabilistic ICER: £58,056
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £21,674 Inc. QALYs: 0.42 ICER: £51,186 Probabilistic ICER: £50,206	Inc. Costs: £21,525 Inc. QALYs: 0.41 ICER: £51,936 Probabilistic ICER: £51,322	Inc. Costs: £21,013 Inc. QALYs: 0.38 ICER: £54,606 Probabilistic ICER: £54,259	Inc. Costs: £20,495 Inc. QALYs: 0.35 ICER: £57,756 Probabilistic ICER: £56,891

Table 9: ERG curve results (exponential) as requested by NICE (including credit)

	Continued treatment effect over lifetime for patient after 2 years stopping rule applied	Continued treatment effect over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect	Continued treatment effect over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect
100% continue treatment after 2 years (no stopping rule)	Inc. Costs: £20,805 Inc. QALYs: 0.29 ICER: £71,614 Probabilistic ICER: £71,473	Inc. Costs: £20,805 Inc. QALYs: 0.29 ICER: £71,622 Probabilistic ICER: £71,891	Inc. Costs: £20,780 Inc. QALYs: 0.29 ICER: £71,880 Probabilistic ICER: £72,255	Inc. Costs: £20,688 Inc. QALYs: 0.28 ICER: £72,652 Probabilistic ICER: £72,758
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £19,750 Inc. QALYs: 0.29 ICER: £67,981 Probabilistic ICER: £68,271	Inc. Costs: £19,749 Inc. QALYs: 0.29 ICER: £67,988 Probabilistic ICER: £67,921	Inc. Costs: £19,725 Inc. QALYs: 0.29 ICER: £68,231 Probabilistic ICER: £68,097	Inc. Costs: £19,645 Inc. QALYs: 0.28 ICER: £68,992 Probabilistic ICER: £68,954
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	Inc. Costs: £19,525 Inc. QALYs: 0.29 ICER: £67,205 Probabilistic ICER: £67,355	Inc. Costs: £19,524 Inc. QALYs: 0.29 ICER: £67,213 Probabilistic ICER: £67,133	Inc. Costs: £19,500 Inc. QALYs: 0.29 ICER: £67,453 Probabilistic ICER: £67,503	Inc. Costs: £19,423 Inc. QALYs: 0.28 ICER: £68,211 Probabilistic ICER: £68,263
0% continue treatment after 2 years (full implementation of the stopping rule)	Inc. Costs: £19,398 Inc. QALYs: 0.29 ICER: £66,769 Probabilistic ICER: £66,758	Inc. Costs: £19,397 Inc. QALYs: 0.29 ICER: £66,777 Probabilistic ICER: £66,770	Inc. Costs: £19,373 Inc. QALYs: 0.29 ICER: £67,015 Probabilistic ICER: £67,567	Inc. Costs: £19,298 Inc. QALYs: 0.28 ICER: £67,772

Extrapolation of PFS

At the request of NICE in the above tables the long-term PFS assumption uses an exponential curve. BMS disagrees with this and believes an alternative curve for PFS is more appropriate. Table 10 presents alternate PFS curves for the intermediary OS curves. All other assumptions in table 3 remain the same.

Table 10: Intermediary results (worst-case scenario) with alternate PFS and TTD curves (including melanoma and RCC credit)

OS	PFS	ICER
Generalized gamma	Weibull	£48,643
Generalized gamma	Gamma	£50,235
	Average ICER	**£49,439**

Conclusion

In order to address the uncertainties identified by the committee, a number of solutions are being proposed to further support the case for the cost-effectiveness of nivolumab in NSCLC. The first of these is to introduce a revised PAS and the second is to include results when a 2-year stopping rule is applied.

The results for these scenarios are presented to reflect both the base-case assumptions submitted by BMS and the intermediary worst-case curve. It is worth noting that these are statistical models and should not be given the same weight as real data. [redacted]

BMS disagree with the need to include additional treatment waning effects because this has already been taken into account in the BMS base-case and so there is no need to add in an additional decrease in OS after 2 years. The size of the decrease in OS at 2 years in the BMS base-case curve is larger than the decrease in OS in CheckMate 003 which has a maximum treatment duration of 96-weeks.

BMS has also been asked to consider scenarios where the 2 year stopping rule is not completely adhered to and these results are included in the tables above. NHSE has been very clear at the recent pembrolizumab NICE appraisal for first line NSCLC that they would not fund treatment beyond 2 years and BMS see no reason why NHSE cannot use the same system for nivolumab. Therefore we believe those scenarios are not relevant to the committee.

BMS have also presented scenarios (Tables 7, 8 and 9) where a credit from melanoma and RCC is applied, an approach consistent with that taken into account in the recent appraisal of pembrolizumab for NSCLC and included in Section 4.18 of the FAD (TA 428)

Adoption of nivolumab for the treatment of NSCLC would represent a step-change in advancing the management of this life-threatening condition and improve long-term survival. Nivolumab for this indication has already been recommended for use in Scotland by the SMC. There still exists a clear unmet need despite the recent NICE approval of pembrolizumab for patients with NSCLC whose tumour expresses PD-L1 at ≥1%. In the paper published from Keynote 010 (Herbst et al) the number of patients that were PD-L1 positive ≥ 1% was 54% of the tested population. This means that approximately 45% of patients with NSCLC would be ineligible for treatment with pembrolizumab, based on a negative or absent test result, and so would be potentially treatable with nivolumab.

[redacted]

		CheckMate 003	CheckMate 057 – Nivolumab arm
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]		[redacted]

Nivolumab for treating squamous and non-squamous non-small-cell lung cancer [ID 811 and 900]

Bristol-Myers Squibb (BMS) believes it is offering a financially attractive, balanced proposal which takes into account and mitigates perceived potential risks to the NHS around variable efficacy due to PD-L1 expression, while at the same time taking significant risks from the BMS perspective based on our understanding and interpretation of our data.

Before responding to your specific questions BMS thought it would be helpful to summarise our key points in response to the uncertainties which have been raised:

- Throughout the appraisals for nivolumab treatment in squamous and Non-Squamous 2L NSCLC we have reviewed in detail and taken into account the uncertainties expressed by the Committee

- The data which we have consistently presented to NICE were for the all-comers populations, most recently 3 year O/S data from our phase 3 trials (CheckMate 017 & 057) and 5 year O/S data from our phase 1 trial (CheckMate 003)

- The commercial proposal which we have presented to NHS England is directly related to the all-comers trial data mentioned above, and has taken the risks to the NHS into account when proposing the level of discount. This has produced plausible ICERs below the £50,000 willingness to pay threshold for 'end of life' qualifying medicines, and as such is aligned with the intent of the new Cancer Drugs Fund (CDF).

- For nivolumab, PD-L1 status is not a robust predictor of response, and testing for PD-L1 status is not fully established. In addition, there are a sizeable number of patients for whom their PD-L1 status is unknown either because of non-viability to biopsy or where the results are uninterpretable

- There is currently an unmet treatment need among 2L NSCLC patients whose PD-L1 status is either unknown or negative. Data collected within the CDF and data maturing in the trials mentioned above will be important in evaluating nivolumab across sub-populations and reducing uncertainty at the end of the CDF period for these indications

- During the two NICE appraisals for nivolumab for NSCLC many stakeholders raised concerns about the Committee making a recommendation which would restrict the use of nivolumab by PD-L1.

- There is also the concern about a lack of consistency at NICE. In the ACD1 for squamous NSCLC the NICE Committee concluded that it was not possible to identify any subgroups for whom nivolumab would provide particular benefits, and so it was

unable to make recommendations for nivolumab in specific subgroups. It is not clear why NICE should now consider a different conclusion.

- The modest budget impact relates to the all-comers populations for both squamous and Non-squamous indications

As requested the cost-effectiveness estimates for the relevant populations for the whole population, PD-L1-positive patients and PD-L1-negative patients are listed separately for squamous and non-squamous groups. These results incorporate the committee's preferred assumptions.

The first set of tables (Table 2 to Table 7) use the discounts in the original CDF proposal (Squamous discount = [redacted] and non-Squamous = [redacted]). This level of discount was accepted from a cost-effectiveness perspective.

BMS understand that within the 4x4 grid the scenario the committee would prefer to make a decision is the lower right hand corner (Continued treatment effect over 3 years for patient after 2 years stopping rule applied with 0% of patients continuing treatment after 2 years (full implementation of the stopping rule), and then no more treatment effect.) There are a large number of ICERs in this document so for simplicity these ICERs under this specific scenario are summarized below (**Table 1**).

Table 1. Summary of decision making ICERs nivolumab versus docetaxel

PD-L1 status	**Squamous**	**Non Squamous**
Discount	[redacted]	[redacted]
All-comers	£49,982	£49,122
<1%	[redacted]	[redacted]
≥ 1%	[redacted]	[redacted]

With both discount levels the "all-comers" ICER is beneath the £50,000 willingness to pay threshold The impact of analysing cost-effectiveness by PD-L1 subgroups is to increase the ICER in the PD-L1<1% subgroups and decrease the ICERs in the PD-L1≥ 1%.

The BMS commercial offer mitigates the risk for recommending for the PD-L1 group <1% as well as the PD-L1≥ 1% expressers because the discount offered by BMS moves the average ICER below the cost-effectiveness threshold. If there is heterogeneity by PD-L1 expression then any theoretical argument which proposes that the all-comers threshold should be lowered due to low expressers potentially having a lower clinical benefit would also have to take into account that this would be offset by the PD-L1 high expressers who may have an above average clinical benefit.

It is also worth noting that the registration phase 3 studies for both indications of nivolumab in NSCLC - CheckMate 017 (squamous) and CheckMate 057 (non-squamous) were not

powered to show a difference between the PD-L1 subgroups; so any conclusions are inherently uncertain. It's also worth noting that when the squamous and non-squamous data is pooled to increase the sample size the hazard ratios (HR) are favourable for both the PD-L1 <1% and PD-L1 ≥ 1% groups (**Overall HR** = 0.72 95% Confidence Interval (CI) 0.62-0.84. **PD-L1 <1% HR** = 0.78 CI 0.61-0.99. **PD-L1 ≥ 1% HR**=0.67 CI 0.53-0.85)

In addition, BMS and much of the clinical community maintain that NICE have underestimated the long-term overall survival (OS) of nivolumab, a sentiment further supported by the 3-year pivotal trial data from CheckMate 017 and CheckMate 057 along with the 5-year data from the CheckMate 003 trial. See Table 8

The OS extrapolation assumption used to determine the final ICERs by NICE is conservative which means that BMS needs to offer a discount to move these ICERs to below the NICE cost-effective threshold. Had an OS assumption closer to the clinical data been selected then a lower discount would be needed.

As well as addressing uncertainty around the potential impact of PD-L1 subgrouping there are uncertainties associated with PD-L1 testing which need to be taken into account when finalizing the NICE recommendation.

- PD-L1 is an imperfect predictive biomarker. Testing methodologies are still being developed, and there is no single standardised test routinely used by the NHS. Although the tests have a high positive predictive value, they also have a low negative predictive value, which means that patients who test negatively can still benefit from treatment.
- Because PD-L1 expression changes over time and varies throughout the tumour, there is a risk of misclassification of patients. PDL-1 status is also subject to sampling error. A host of other mediators in the tumour microenvironment determine response to checkpoint blockade and as yet are poorly understood. Which explains the phenomenon that patients with 2L NSCLC having PD-L1 expression levels <1% still respond to treatment with anti-PD1 agents and some achieve complete response.
- Archival tissue from time of diagnosis may not be an accurate representation of PD-L1 status at time of treatment and a repeat biopsy carries significant risk in these patients with pre-existing lung co-morbidities. In some patients it will not be possible to achieve a PDL-1 status as a biopsy will not be viable.
- In addition to BMS many stakeholders to the two appraisals raised concerns about the Committee making a recommendation which would restrict the use of nivolumab by PD-L1.

In addition, to scientific arguments against a PD-L1 restriction, there is also the concern about a lack of consistency at NICE. In the ACD1 for squamous NSCLC (issued 15th Dec 2015), it states in Section 4.5 that the PD-L1 subgroup analyses in CheckMate-017 provided no evidence of a significantly different effect in any of the subgroups assessed, including the proposed biomarker: PD-L1. The NICE Committee highlighted that PD-L1 expression status

is dynamic and can change over time; it therefore considered that these results should be viewed with caution. The Committee concluded that it was not possible to identify any subgroups for whom nivolumab would provide particular benefits, and so it was unable to make recommendations for nivolumab in specific subgroups. It is not clear why NICE should now consider the opposite conclusion.

CONCLUSION

BMS have presented an attractive and balanced CDF proposal which is associated with cost-effectiveness ICERs which are below the £50,000 threshold for all patients regardless of PD-L1 expression level. BMS has already de-risked this proposal by using OS extrapolations far more conservative than what the long-term trial data supports. The impact of analysing cost-effectiveness by PD-L1 subgroups shows that any risk associated with making an all comers recommendation is mitigated by the proposal made by BMS.

Adoption of nivolumab for the treatment of NSCLC would represent a step-change in advancing the management of this life-threatening condition and improve long-term survival. Nivolumab for this indication has already been recommended for use in Scotland by the SMC for all patients regardless of PD-L1 expression level. There still exists a clear unmet need despite the recent NICE approval of pembrolizumab for patients with NSCLC whose tumour expresses PD-L1 at ≥1%. In the paper published from Keynote 010 (Herbst et al) the number of patients that were PD-L1 positive ≥ 1% was 54% of the tested population. This means that approximately 45% of patients with NSCLC would be ineligible for treatment with pembrolizumab, based on a negative or absent test result, and so would be potentially treatable with nivolumab.

Table 2. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [All-comers]

OS: Generalised gamma 3Y **PFS: ERG hybrid Exponential**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
8% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [≥ 1% PD-L1 Subgroup]

OS: Generalised gamma 3Y **PFS: ERG hybrid Exponential**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
8% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [<1% PD-L1 Subgroup]

OS: Generalised gamma 3Y **PFS: ERG hybrid Exponential**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
8% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [All-comers]

OS: Hybrid Exponential 3Y **PFS: ERG hybrid Exponential**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [≥1% PD-L1 Subgroup]

OS: Hybrid Exponential 3Y **PFS: Hybrid Exponential 2Y**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Cost-effectiveness results for nivolumab compared with docetaxel for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [<1% PD-L1 Subgroup]

OS: Hybrid Exponential 3Y **PFS: ERG hybrid Exponential**	**Continued treatment over lifetime for patient after 2 years stopping rule applied**	**Continued treatment over 10 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 5 years for patient after 2 years stopping rule applied, and then no more treatment effect**	**Continued treatment over 3 years for patient after 2 years stopping rule applied, and then no more treatment effect**
100% continue treatment after 2 years (no stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]
25% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
9% continue treatment after 2 years (no stopping rule, or implementation of a stopping rule but some patients do continue)	[redacted]	[redacted]	[redacted]	[redacted]
0% continue treatment after 2 years (full implementation of the stopping rule)	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 Comparison of data versus modelled survival

Data Source	Curve	Proportion Alive at each year						
		1	2	3	4	5	10	15
Squamous								
CheckMate 017		42.2%	23.0%	[redacted]	[redacted]			
CheckMate 003		42%	24%	18%	16%	16%		
Model estimates for nivolumab OS	BMS Log-logistic	42.34%	23.53%	16.08%	12.17%	9.77%	4.90%	3.26%
	Intermediary Generalised gamma	43.31%	22.56%	13.53%	8.82%	6.08%	1.51%	0.55%
	Fully Exponential	42.22%	23.25%	11.79%	6.23%	3.30%	0.14%	0.01%

Data Source	Curve	Proportion Alive						
		1	2	3	4	5	10	15
Non-squamous								
CheckMate 057		50.7%	28.7%	[redacted]	[redacted]			
CheckMate 003		42%	24%	18%	16%	16%		
Model estimates for nivolumab OS	BMS Log-normal	46.78%	27.78%	18.75%	13.61%	10.35%	3.83%	1.93%
	Intermediary Generalised gamma	47.64%	27.35%	17.58%	12.08%	8.70%	2.47%	0.98%
	Fully Exponential	51.61%	26.63%	13.74%	7.09%	3.66%	0.13%	0.00%

*represent censored observations

Final queries prior to 15 August 2017 committee meeting: Nivolumab - NSCLC [ID811 & ID900]

(Response from BMS 9th Aug 2017)

1. **Provide BMS' explanation for the difference in the HRs in the different subgroups of PD-L1 expression for the squamous indication (ID811). According to the forest plot figures by PD-L1 expression level, in the company submission (Figure 12 of the original submission for squamous NSCLC), the HRs show higher effectiveness for the subgroups with the lowest PD-L1 expression cut-off point compared with other subgroups.**

The forest plots are from the registration studies for the squamous and non-squamous population (CheckMate 017 and 057) which were powered to show superiority over docetaxel in patients with relapsed advanced metastatic NSCLC. They were not powered to show a difference by PD-L1 expression. Any interpretation of these sub-group analyses by PD-L1 expression must therefore be considered indicative at most.

In addition, there are reservations around using this biomarker. Testing methodologies are still being developed, and there is no single standardised test routinely used by the NHS. Although the tests have a high positive predictive value, they also have a low negative predictive value, which means that patients who test negatively can still benefit from treatment. In addition, because PD-L1 expression changes over time and varies throughout the tumour, there is a risk of misclassification of patients. PDL-1 status is also subject to sampling error.

Nivolumab is a proven effective treatment option versus docetaxel in this patient population regardless of PD-L1 expression and this has been reflected in the EMA licence when they considered the benefit/risk profile of nivolumab.

BMS understands the rationale behind the CDF is to enable patient access to innovative medicines whilst allowing time for additional data to be generated to investigate uncertainties identified by NICE. In these two NSCLC nivolumab appraisals uncertainty has been identified in the long-term survival and whether PDL1 expression has an impact on patient outcomes. The CDF proposal BMS has outlined will collect data to address both of these and we believe the commercial deal addresses the risk during the 2 year CDF period whilst allowing patient access to an important EAMS medicine.

2. **We note that there were ~20% of patients in the trials with an unquantifiable PD-L1 expression level, so please explain whether/how this group is represented in the HR results.**

The results from this sub-group of patients within both clinical trials (CheckMate 017 and 057) were not included in the latest results sent to NICE. There was no guidance what to do with this group so we undertook the simplest approach and excluded them from the analysis. We believe inclusion of these patients to either group would have improved the HR and would would have further improved the cost-effectiveness. Exclusion of them should therefore be considered a conservative estimate.

3. **Also provide BMS' explanation of the relationship between the clinical observations in 1. And the corresponding cost-effectiveness results for all subgroups for the squamous indication.**

Answered as part of response 1

4. **Explain the reason for BMS choice of a 1% cut-off point for formulating subgroups based on PD-L1 expression level (acknowledging that in the ACD2 for both indications (i.e. squamous and non-squamous) the committee was minded not to recommend nivolumab for NSCLC in adults with a PD-L1 expression of 10% or greater, but to invite BMS to submit a proposal for inclusion in the CDF)**

The request from NICE on the 7th July for stratification of cost-effectiveness results by PD-L1 status requested "Specifically, results need to be separately presented for the whole population, PD-L1-positive patients and PD-L1-negative patients in both the squamous and non-squamous groups."

Within the recent pembrolizumab appraisal [TA428] for the same therapy area it uses a PD-L1 expression of 1% or more as the definition for a PD-L1 "positive" expresser. This is also in-line with the on-going appraisal of nivolumab for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971].

BMS therefore assumed that the request was to use a PD-L1 expression level of 1% or more to define "positive".

Within the request from the 7th July a particular PD-L1 expression level was not stated anywhere.

5. **NICE request further evidence about the number of patients eligible for nivolumab in the different subgroups by PD-L1 expression in the NHS in England and BMS' rationale of how the different subgroups will be treated in practice.**

It is estimated that the split between PD-L1 positive patients is 55% and PD-L1 negative patients (and those that have an unknown status) is 45%. [Herbst RS, et al. Lancet 2015; 387(10027):1540-50.] These numbers demonstrates the huge unmet need that exists in England in regards to the number of patients that would be ineligible for treatment with pembrolizumab.

In order to understand how different subgroups could be treated in practice in England we need to consider which other therapies are available to the NHS for previously treated NSCLC patients.

Pembrolizumab has a similar mode of action to nivolumab but is licensed only for those patients with tumours expressing PD-L1 ≥1%.

Another key difference between the nivolumab NSCLC and the pembrolizumab NICE appraisal is that nivolumab has been separated by histology into two appraisals, whereas the pembrolizumab appraisal was not been split by histology.

In order to have a sense of the relative effectiveness the pooled analysis of CheckMate 057 and -017 can be used. In the pooled analysis of CheckMate 017 and 057 the median OS with nivolumab in PD-L1 ≥1% patients was 13.4 months vs 8.5 months for docetaxel (HR: 0.67; 95% CI: 0.53–0.85). In KEYNOTE-010, the median OS for the PD-L1 ≥1% population treated with pembrolizumab was 10.4 months vs. 8.5 months for docetaxel (HR: 0.71; 95% CI: 0.58-0.88; p=0.0008). [Herbst RS, et al. Lancet 2015; 387(10027):1540-50.]

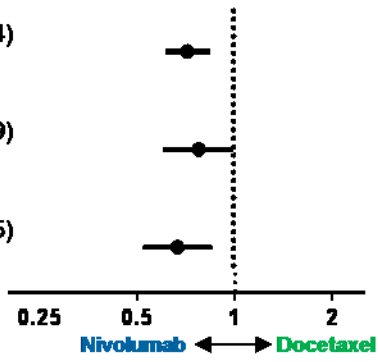
This is an unadjusted comparison, however the results in the PDL1 ≥1% population are more favorable to nivolumab than for pembrolizumab. Based on this one could therefore argue that

within the PDL1 ≥1% population there is a clinical rationale to prefer nivolumab to pembrolizumab.

Nivolumab is not currently available for use within NHSE so the relative use of nivolumab and pembrolizumab are unknown. However, both therapies are available for NSCLC within the US. From the most recent Chart Audit data (June 2017) of the patients with PD-L1 expression ≥1% approximately 31% of new 2L NSCLC patients receive nivolumab monotherapy and within the PDL1 <1% patients approximately 58% of new 2L NSCLC patients receive nivolumab mono. There is more use within the PDL1 <1% population, but when a weighted average ICER is calculated the all-comers ICER of nivolumab versus docetaxel for Squamous is £47,888 and for Non-Squamous £48,641. This indicates that if UK usage was to mirror usage in the US then the use of nivolumab would be cost-effective. This provides further reassurance that the CDF proposal reduces the risk to the NHS.

The different efficacy by PD-L1 subgroup of nivolumab within the pooled analysis is shown below. This can be compared with the analysis for pembrolizumb and provides further rationale why the impact of PD-L1 expression is not obvious and warrants further investigation within the CDF.

	Nivolumab		Docetaxel		
PD-L1 expression	n	mOS (95% CI)	n	mOS (95% CI)	HR (95% CI)
Overall	427	11.1 (9.2, 13.1)	427	8.1 (7.2, 9.2)	0.72 (0.62, 0.84)
<1%	162	9.6 (7.6, 13.3)	153	7.8 (6.7, 10.5)	0.78 (0.61, 0.99)
≥1%	186	13.4 (10.3, 17.5)	179	8.5 (7.0, 9.3)	0.67 (0.53, 0.85)



6. **Provide BMS rationale for the difference in clinical effectiveness results (HRs) between the squamous and non-squamous appraisal topics?**

There are limitations when making cross-study comparisons; however, nivolumab showed significant improvement in OS in both SQ (CheckMate 017) and NSQ (CheckMate 057) NSCLC patients.

It is widely accepted that SQ and NSQ NSCLC may indeed be different diseases (with SQ NSCLC being the more aggressive sub-type as are all other squamous cancers originating in any other organ). For example, NSQ NSCLC is largely driven by single driver mutations in e.g., the EGFR and ALK genes, whereas SQ NSCLC is considered to be a much more complex disease with multiple mutations and other genetic changes largely induced by tobacco. These and other biological differences are reflected in the different outcomes between SQ and NSQ NSCLC with different therapies.

7. **Confidentiality - all the tables with costs and QALYs marked CiC for all comers, including the ICERs are marked. This is not in line with what we agreed at the last meetings for squamous and non-squamous, where the incremental costs and QALYs and the ICERs were**

shown in part 1. So we request that the ICERs at the very least are 'unmarked' for the slides and post-committee documentation to show decision-making (even though the meeting will be in private part 2 only).

During the discussion with NICE on 4th July when the request for undertaking this PD-L1 sub analysis was initiated, it was made clear on the call that the ICERs would be used confidentially. The clinical data they are based on is unpublished and the nivolumab discount is confidential and pending NHSE approval. In the event of the CDF proposal not being accepted, the discount will not be agreed so the ICER is moot and so there is no need to publish it. If the CDF proposal is accepted, then the key concern is preventing back calculation of the confidential discount.

In the interest of best use of resources, BMS suggest we pause this discussion until after the Committee has made a decision and we know what details are needed for the public documents.

8. **In line with NICE processes, committee will not consider the BMS analyses including the arrangements for VAT adjustment, so please delete all results and reference to VAT in your submission documents and cost-effectiveness results, readjusting your conclusions appropriately, and re-submit updated documents and models for both squamous and non-squamous appraisal topics.**

Further queries prior to 15 August 2017 committee meeting: Nivolumab - NSCLC [ID811 & ID900]

(Response from BMS 10th Aug 2017)

Question 1. In the model for non-squamous NSCLC (ID900), how was the hybrid exponential approach implemented on the 3 year data? How was the breakpoint chosen? Please explain why the HRs for all-comers are higher than both the HRs for ≥1% PD-L1 and >1% PD-L1 subgroups.

Based on the description in the original ERG report as well as additional information gleaned from the various meetings and reports, we understand that the ERG fitted an exponential curve to the Kaplan Meier data from a specific point in time – 8 months.

The ERG recommended that an appropriate time to commence the extrapolation was at the time of perceived linearity from the cumulative hazard plots.

BMS have concerns regarding this choice of time point as this is subject to interpretation, and sensitivity analysis when using alternate time points which appear to make a significant difference to the ICERs (in favour of nivolumab).

For the purpose of the request on the 7th July 2017, we provide the results using the ERG's recommended time point of 8 months for the all-comers population so the analysis was like-for-like.

This was not feasible for the PDL1 subgroups because the small patient populations made this unstable. So instead a cut-point of 27 months was used for the PD-L1 subgroups. This was based on visual inspection of the all-comers hazard rate over time and looked the most appropriate break point. With more time, BMS would have used a more statistical approach to identify the break point (likely the Chow test).

Question 2. Please clarify why the HR from the docetaxel arm is applied to patients on the nivolumab arm after the end of the nivolumab treatment effect.

This was agreed back in March 2017 and has been in the model since then. We assumed equal hazard ratio between nivolumab and docetaxel when no more treatment effect is applied in the model. BMS don't believe there needs to be this waning effect however in the interest of progressing with the appraisal we conceded this point.

Question 3. Please justify the difference between the breakpoints for the hybrid exponential approach for PFS between all comers and the subgroups.

As discussed in question 1 above different break points are used to accommodate the smaller populations for the PD-L1 subgroups and the lack of data in the tail of the Kaplan-Meier curve. With more time, BMS would have used a more statistical approach to identify the break point (likely the Chow test).

CRITIQUE OF THE NEW ANALYSES FOR NIVOLUMAB FOR SQUAMOUS AND NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

11th of August 2017

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About the Decision Support Unit

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its DSU. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Bermejo I. Critique of the new analyses for nivolumab for squamous and non-squamous non-small cell lung cancer. School of Health and Related Research (ScHARR), 2017.

Use of confidential data

Any 'commercial in confidence' data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any 'academic in confidence' data provided by the company, and specified as such, is highlighted in yellow and underlined in the review.

EXECUTIVE SUMMARY

The company presented new analyses for nivolumab for squamous and non-squamous non-small cell lung cancer (NSCLC) including a new Patient Access Scheme and subgroup analyses of patients with PD-L1 ≥1% and patients with PD-L1 < 1%. These analyses were conducted using an updated version of the models where: the most recent cut of the survival data (3 years) was used; and, the hybrid exponential approach preferred by the appraisal committee (AC) was implemented to extrapolate overall survival (OS) in the model for non-squamous NSCLC.

The company's implementation of the hybrid exponential for the extrapolation of OS for non-squamous NSCLC is significantly different to that used by the Evidence Review Group (ERG) and it is unclear how big an impact the differences between the two approaches have in the analysis. In addition, considerable uncertainty remains in the company's analyses for the full population given that: (i) assumptions on the stopping rule and the duration of the post-discontinuation treatment effect are not based on evidence from a trial but subjective estimation; (ii) there is still considerable uncertainty on the estimation of OS, which has a strong impact in the results; and, (iii) for non-squamous NSCLC, the relevant comparator nintedanib plus docetaxel has been excluded from the analyses.

In the subgroup analyses, the uncertainty around the estimation of OS and progression free survival (PFS) is higher due to smaller sample sizes. This issue especially affects the estimates using the hybrid exponential approach, due to the lack of stability of the hazard function at the tail of the Kaplan-Meier curve, which determines the extrapolation.

The DSU believes that the company's analyses contain two errors: (i) when the curves for PFS and OS cross, OS is corrected to be as high as PFS instead of correcting PFS to be as high as OS; and, (ii) the waning of the treatment effect after discontinuation does not affect PFS, but only OS. Correcting for these errors especially affects the subgroup of patients with PD-L1 ≥ 1%, for which the incremental cost-effectiveness ratios (ICERs) of nivolumab versus docetaxel increase from [redacted] to [redacted] per QALY and from [redacted] to [redacted] per QALY in patients with squamous and non-squamous NSCLC respectively.

1. INTRODUCTION

The company submitted new evidence and analyses for the ongoing Single Technology Appraisals (STAs) of nivolumab for squamous and non-squamous non-small cell lung cancer (NSCLC). In its analyses, the company included [redacted] for squamous and non-squamous NSCLC respectively.

The company presented cost-effectiveness results for two separate subgroups for both of the appraisals: patients with PD-L1 ≥1% and patients with PD-L1 < 1%. The analyses were undertaken after:

- incorporating the 3 year data cut of the two pivotal trials (CheckMate 017 and CheckMate 057), and
- correcting the modelling of overall survival (OS) for non-squamous NSCLC to reflect the preferences of the Appraisal Committee (AC).

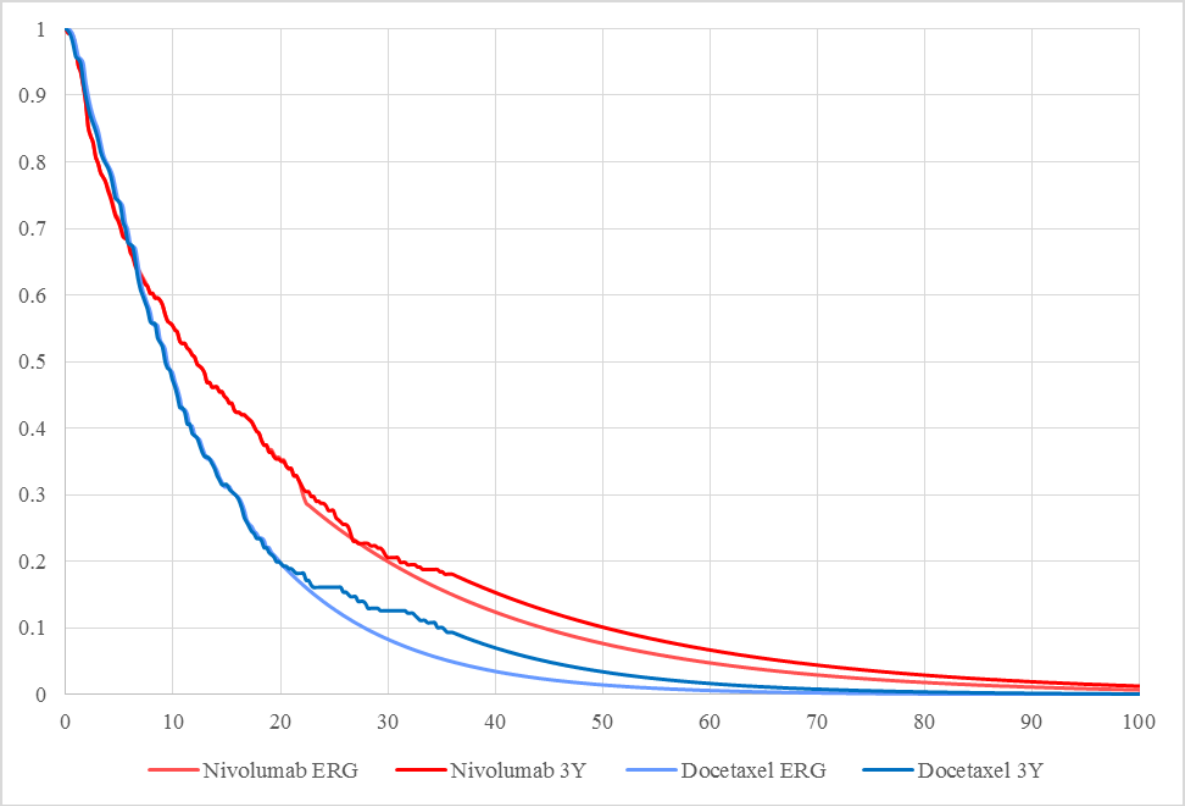
2. CRITIQUE OF THE NEW EVIDENCE

2.1. IMPLEMENTATION OF AC-PREFERRED OS EXTRAPOLATION FOR NON-SQUAMOUS NSCLC (ALL COMERS)

The company implemented the hybrid exponential approach for the extrapolation of OS for the non-squamous population as preferred by the AC and incorporating the last cut of the survival data (3 years). For this purpose, the company calculated a constant hazard based on the Kaplan Meier (KM) data from 8 months onwards and justified this approach referring to the Evidence Review Group's (ERG) implementation [1]. However, the ERG's implementation contains substantial differences: the ERG identified two subgroups of patients – those who had been treated with nivolumab post-progression and those who had not – and calculated the hazard for each of the subgroups beyond around 7 months [2]. Another substantial difference between the company's and the ERG's approach was that the former used the KM data up to month 36 and then used the constant hazard to extrapolate OS whilst the latter established the breakpoint at around 18 months and then used a mixed exponential model based on the assumption that 25% of patients would receive treatment post-progression. The company did not provide sensitivity analyses to assess how the choice of the breakpoints (8 months and 36 months) impacts the results of the analysis.

The plot in Figure 1 shows a comparison of the hybrid exponential OS extrapolation produced by the ERG with the 18 month data cut and the one produced by the company with the 3 year data cut. The differences between these two approaches are likely to be mostly explained by the more mature survival data used by the company in their new analyses but it is unclear how much the company's extrapolation would be impacted had they used the same approach used by the ERG.

Figure 1: Comparison of hybrid exponential OS extrapolations estimated by the ERG and the company (non-squamous, all comers)



2.2. PD-L1 SUBGROUP ANALYSIS

The company presented results for two subgroups: patients with a PD-L1 ≥1% and patients with a PD-L1 <1%. The subgroup analyses were based on subgroup-specific OS and progression-free survival (PFS) curves. For PFS, the company used the hybrid exponential approach for the populations with squamous and non-squamous NSCLC, as favoured by the AC for the full populations. For OS, the company used the hybrid exponential approach for the non-squamous NSCLC population and a generalised gamma for the squamous NSCLC population, as favoured by the AC for the respective full populations.

The company acknowledged issues when trying to apply the hybrid exponential to the subgroups. Due to relatively small sample sizes (patient numbers per arm in the squamous NSCLC population ranged from 52 to 63 and from 101 to 123 in the non-squamous NSCLC population), the hazard was deemed unstable throughout most of the available survival data and a breakpoint of 27 months was used for OS. The choice of the breakpoint at 27 months was deemed by the company to be appropriate upon visual inspection of the all-comers hazard. However, the company did not present sensitivity analyses to assess the impact of using a different breakpoint on the results of the analyses. Therefore, the KM curve was used to estimate the proportion of patients alive for the first 27 months and a constant hazard was applied thereafter. This hazard was calculated based on the tail of the KM curve, namely on the events happening after 27 months. The number of subjects at risk at this time was very low (ranging from 14 to 37) and most patients were censored after 36 months. Therefore, the estimation of the constant hazard applicable to patients after the breakpoint is subject to high uncertainty. In the case of patients with PDL-1 ≥ 1% and non-squamous NSCLC, a plateau in the KM curve between [redacted] as shown in Figure 2 has a strong impact in the calculation of a very low hazard rate, which is used to extrapolate OS for the remaining of the time horizon.

Figure 3 shows how the resulting extrapolation of OS and the stark contrast between the periods before and after the breakpoint.

Figure 2: Kaplan-Meier curve of OS for the PD-L1≥1% subgroup in the CheckMate 057 trial of patients with non-squamous NSCLC (reproduced from [3])

Figure 3: OS extrapolation for patients with PDL-1 ≥ 1% and non-squamous NSCLC

The extrapolation of PFS in patients with squamous and non-squamous populations was subject to the same issues, which leads to implausible results such as those produced for patients with with PD-L1 ≥1% and squamous NSCLC. Figure 4 shows the KM curve and the extrapolation of the PFS for the nivolumab and docetaxel arms. The likely overestimation of PFS for nivolumab results in the PFS and OS curves crossing between [redacted], when both are just below [redacted] as shown in Figure 5.

Figure 4: KM and extrapolation of PFS curves for patients with PD-L1 ≥1% and squamous NSCLC

Figure 5: OS and PFS curves for patients with PD-L1 ≥1% and squamous NSCLC (time in years)

2.3. ADDITIONAL CRITIQUE

2.3.1. Implementation of the stopping rule and end of treatment effect

The model assumes that after the stopping rule is applied, the patients on nivolumab incur in no additional treatment costs but keep enjoying the benefits in terms of PFS and OS while the treatment effect lasts. After the treatment effect has waned, which in the base case is assumed to last 3 years after treatment discontinuation, the mortality rate of docetaxel is applied to these patients. The DSU notes that these patients are no longer receiving treatment and therefore it would be more appropriate either to apply the mortality rate of best supportive care or to include the costs and adverse events applicable to a docetaxel treatment, unless it is accepted that treatment effect does not wane completely and the residual treatment benefit is analogous to that of docetaxel. The DSU also notes that the waning of the treatment effect is only applied to OS and it should also be applied to PFS. In order to be consistent, patients on PFS after the end of treatment effect should progress to the progressed disease state at the same rate of docetaxel.

Finally, the DSU notes that in the appraisal of nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy, the AC concluded that, given the uncertainty about the stopping rule, it would only consider analyses without the stopping rule to inform its recommendations [4].

2.3.2. Missing comparator for the non-squamous population

In their latest submission, the company only presented incremental cost-effectiveness ratios (ICERs) for nivolumab versus docetaxel. However, as concluded by the AC[5], nintedanib plus docetaxel is also a relevant comparator in patients with non-squamous NSCLC. Nintedanib plus docetaxel is recommended by NICE for patients for treating NSCLC of adenocarcinoma histology, which constituted 90% of patients in the CheckMate 057 trial[6].

2.3.3. Crossing PFS and OS curves

In the company's model, when the PFS and OS curves cross, OS is corrected to be as high as PFS. On the contrary, PFS should be corrected never to be higher than OS, given that the estimation of OS is less uncertain than that of PFS.

2.4. RESULTS

The company presented a summary of ICERs for nivolumab versus docetaxel as shown in Table 1. For their base case, the company assumed all patients would stop nivolumab treatment after 2 years, after which the treatment effect would last for additional 3 years.

The DSU notes that the ICERs of patients with PD-L1 ≥ 1 [redacted] than those with PD-L1 <1% for both squamous and non-squamous NSCLC. The difference in the ICERs for non-squamous NSCLC across subgroups ([redacted] and [redacted]) is explained by the considerable difference in the efficacy of nivolumab versus docetaxel in terms of OS, as shown in the KM curves presented by the company [3]. [redacted], in patients with squamous NSCLC, the hazard ratio (HR) for nivolumab versus docetaxel [redacted] in patients with PD-L1 <1% than in patients with PD-L1 ≥1% ([redacted] and [redacted] respectively) and [redacted] for nivolumab versus docetaxel [redacted] the latter subgroup. This [redacted] result is mostly explained by the remarkable difference between the PFS curves in the nivolumab and docetaxel arms in patients with PD-L1 ≥1% and squamous NSCLC mentioned in Section 2.2.

Table 1: ICERs for nivolumab versus docetaxel assuming a stopping rule at 2 years and a treatment effect lasting 3 additional years

	Squamous	**Non-squamous†**
All-comers	£49,982	£49,122
PD-L1 <1%	[redacted]	[redacted]

PD-L1 ≥ 1%	[redacted]	[redacted]

†Nintedanib plus docetaxel is also recommended for patients with adenocarcinoma histology

3. EXPLORATORY ANALYSES UNDERTAKEN BY THE DSU

The DSU undertook exploratory analyses after applying two changes to the company's model:

- When the OS and PFS curves cross, cap PFS to OS
- After the end of treatment effect, apply to patients on the nivolumab arm the hazard rate on the docetaxel arm also to PFS

In the results of the exploratory analyses undertaken by the DSU, the ICER for nivolumab compared with docetaxel is considerably higher in patients with PD-L1 ≥ 1% and squamous NSCLC as shown in Table 2. It is worth noting that the ICERs for nivolumab versus docetaxel in both subgroups of squamous NSCLC are higher than that of all-comers. This might be explained by the fact that not all patients in the all-comers populations are included in the two subgroups but more likely due to the uncertainty on the estimates produced for the subgroups.

Table 2: ICERs for nivolumab versus docetaxel for the exploratory analyses undertaken by the DSU

	Squamous	**Non-squamous†**
All-comers	£50,014	£49,160
PD-L1 <1%	[redacted]	[redacted]
PD-L1 ≥ 1%	[redacted]	[redacted]

†Nintedanib plus docetaxel is also recommended for patients with adenocarcinoma histology

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