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)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Bristol-Myers Squibb Pharmaceuticals**
   - **Roy Castle Lung Cancer Foundation**
   - **National Lung Cancer Forum for Nurses**
   - **Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists and National Cancer Research Institute joint comment**
   - **Boehringer Ingelheim**

   'No comment' response received from the Department of Health

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

   Evidence Review Group addendum to the company ACD response – to follow

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

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

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

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Single Technology Appraisal

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

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Bristol-Myers Squibb (BMS)	**EXECUTIVE SUMMARY** In the Appraisal Consultation Document (ACD) issued by NICE, nivolumab is not recommended for treating locally advanced non-squamous NSCLC in adults whose disease has progressed after chemotherapy (NICE, 2016a). Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) disagrees with the proposed recommendation for nivolumab in previously treated locally advanced or metastatic non-squamous NSCLC and provides its comments by section of the ACD below, with a focus on whether the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence and whether the provisional recommendations are a sound and suitable basis for guidance to the NHS. In addition, data from the 24-month data cut of CheckMate 057 are now available (Borghaei et al., 2016) and presented below, including revised cost-effectiveness data based on the 24-month clinical outcomes. Finally, a revised patient access scheme (PAS) has been submitted and the cost-effectiveness results including the PAS are presented in a separate Appendix. The committee acknowledged that despite recent advances in treatments, the prognosis in terms of survival in NSCLC has not substantially improved in the last 30 years (Cancer Research UK, 2015) and recognised that there is need for effective treatment, which are not associated with high toxicity. In addition, the committee consider nivolumab to be an innovative treatment and a step-change in managing non-squamous NSCLC due to its novel mechanism of action, which is associated with fewer toxicities than the currently available treatment options; docetaxel and nintedanib plus docetaxel. The committee also acknowledged that BMS made nivolumab available via an Early Access to Medicines Scheme (EAMS) (NICE, 2016a); approximately 99 patients receiving treatment via EAMS. The following key areas are those in which BMS believe the summaries of clinical and cost-effectiveness are not reasonable interpretations of the evidence, and thus the appraisal committee's recommendations are not sound. **Long-term overall survival benefit of nivolumab**. The appraisal committee has accepted the evidence review group (ERG) assumption that hazards for overall survival (OS) are constant after an initial treatment period in all oncology indications and treatments (NICE, 2016a). However, evidence shows that for immuno-oncologics, long-term survival is possible, and that while an assumption of constant hazards might be reasonable for chemotherapy, it is unclear that this would apply in the same way for immuno-oncologics (NICE, 2016b). In particular, it is important to note that:	Comment noted.

Consultee	Comment [sic]	Response
	• Decreasing hazards are seen over time (as demonstrated in NSCLC patients in CheckMate 003 – Figure 1), suggesting that some long-term survivors will die of natural causes, rather than NSCLC (Bristol-Myers Squibb, 2016a); long-term survival has been observed with immuno-oncologics in a variety of therapeutic settings, including melanoma (treated with ipilimumab, nivolumab or pembrolizumab) and NSCLC (for nivolumab)(Figure 2 and Figure 3)(Bristol-Myers Squibb, 2015; Hodi, 2016; Schadendorf et al., 2015), demonstrated by the development of a 'plateau' in Kaplan-Meir survival curves. Currently the longest median follow-up we have for nivolumab in non-squamous NSCLC from the CheckMate 057 study is 24 months(Borghaei et al., 2016), which may be too early to see the change in curve seen across other indications. Therefore, and similarly to the assumptions in the appraisal for pembrolizumab in melanoma, we anticipate that once the data mature, the same reduction in mortality will be seen for nivolumab in non-squamous NSCLC. • We maintain that CheckMate 003 supports the assumption that long-term survival can occur in patients with advanced NSCLC treated with nivolumab, considering the similar trends in OS for nivolumab in CheckMate 057 and CheckMate 003 (Bristol-Myers Squibb, 2016b). Paying no consideration to the CheckMate 003 study is unreasonable since it provides the longest follow-up data available to date and shows a notably similar trend in OS for nivolumab when compared with CheckMate 057. Further, patients in CheckMate 003 had metastatic NSCLC at trial entry and similar baseline patient characteristics to patients in CheckMate 057 and ORR in the two studies was similar, as was median duration of response (DOR). For a number of reasons (described in detail below), OS at 3 and 4 years in the CheckMate 057 cohort could be expected to be equal to, or above, that of CheckMate 003. • New 24-month data from CheckMate 057 continue to support the possibility of long-term survival (Borghaei et al., 2016). Validation of the survival analyses in the BMS base-case and the ERG's approach against the 24-month data shows that the data are still consistent in line with the previous extrapolations (Figure 6)(Bristol-Myers Squibb, 2016a). The Appraisal Committee's acceptance of the ERG approach to survival extrapolation is not a reasonable interpretation of the available clinical evidence and clinical expert opinion (NICE, 2016a). Therefore, we request that the Committee considers alternative extrapolations which capture the long-term benefit of nivolumab. **Comparison with nintedanib + docetaxel**. The ERG conducted an unadjusted comparison between nivolumab and nintedanib on the assumption that the docetaxel arms of the two studies are comparable (NICE, 2016b). However, conducting an unadjusted comparison does not respect the randomisation of the trials and therefore goes against current recommendations. In addition, comparing the baseline characteristics of the docetaxel arms in the two studies shows that there are differences in the patient populations which invalidate the ERG's unadjusted comparison (Borghaei et al., 2015; Reck et al., 2014). We therefore consider that our adjusted approach is more appropriate.	

Consultee	Comment [sic]	Response
	Use of progression-free survival (PFS) and time to treatment discontinuation (TTD) to model the PFS health state. In the BMS base-case, TTD was used to model the PFS health state due to the assumption that patients who are treated with nivolumab post-progression continue to receive a clinical benefit (Bristol-Myers Squibb, 2016a). The ERG criticised this and said that PFS should be used to model outcomes and TTD to model costs. We reiterate the evidence that patients on nivolumab continue to gain benefit when treated beyond progression and contend that applying a low utility (for progressed disease) to these patients is not appropriate in the light of available data. **Assessment of utility**. The Appraisal Committee has accepted the ERG's use of the van den Hout et al. (2006) study to calculate utilities for the progressed disease (PD) health state (0.476)(NICE, 2016a). We argue that the patient population in van den Hout et al. (patients with stage III or IV NSCLC, PS2 treated with palliative radiotherapy) is not the same as that in CheckMate 057 and highlight the utility for PD accepted in the nivolumab squamous NSCLC appraisal (0.509)(NICE, 2015a), in the recent nintedanib in NSCLC appraisal (0.64)(NICE, 2015b) and in the erlotinib and gefitinib in NSCLC appraisal (0.47 independent of treatment)(NICE, 2015c) and argue that those accepted in the reviews of nivolumab in squamous NSCLC and nintedanib are likely to be more appropriate than the current committee preferred ERG estimate. In order to ensure the impact of end-of-life is included in the utility estimates, a disutility can be applied to the utility seen in CheckMate 057, based on that from van den Hout (2006), and applied only to the last stage of PD. **Revised cost-effectiveness analysis based on 24-month data from CheckMate 057**. BMS has considered the recommendations of the ERG, the findings of the Appraisal Committee and the newly available 24-month data cut from CheckMate 057 and we have provided a new base-case cost-effectiveness analysis (Bristol-Myers Squibb, 2016c). Changes proposed by the ERG including minor corrections have been incorporated and other changes have been made in line with our response to specific ERG and appraisal committee concerns. This includes new long-term survival extrapolations based on the 24-month CheckMate 057 data and a revised utility in the PFS health state that incorporates a disutility for end-of-life (Bristol-Myers Squibb, 2016c). With the revised model, the ICER using the BMS base case OS extrapolation is £107,000 vs docetaxel and £178,000 vs nintedanib + docetaxel. Deterministic sensitivity analysis revealed that in the comparison with docetaxel, the model was most sensitive to the average body weight and discount rates; in the comparison with nintedanib, the hazard ratio for OS had the greatest impact. **Concluding remarks** Nivolumab is an innovative treatment option that offers a survival and HRQoL benefit as well as reduced toxicity to patients with non-squamous NSCLC who have received prior therapy. This represents a remarkable further advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. In consideration of the proposed PAS (results provided in Appendix), Nivolumab is a cost effective treatment option for patients with non-squamous NSCLC who have received prior therapy.	

Consultee	Comment [sic]	Response
BMS	**2.1 EARLY ACCESS TO MEDICINES SCHEME** As set out in the ACD, nivolumab has been available for the treatment of NSCLC through an EAMS. To date, 284 applications have been made through the EAMS process for nivolumab in PD-L1 mutation positive non-squamous NSCLC; of these, 99 have received treatment with nivolumab.	Comment noted.
	4.3 AND 4.7 LONG TERM OVERALL SURVIVAL BENEFIT OF NIVOLUMAB While the appraisal committee recognised some long-term overall survival benefit from nivolumab they were not persuaded that the trial data supported a decrease in the rate of mortality with nivolumab to the extent suggested by our survival extrapolation (see 4.7 below)(NICE, 2016a). They also considered that CheckMate-003 did not support this comparative advantage of nivolumab over docetaxel. The committee therefore concluded that the ERG's approach to extrapolation (applying an exponential curve that assumed a constant hazard of death from 12 months) was more appropriate (NICE, 2016a). The evidence review group (ERG) have argued that they have (unpublished) evidence that shows that a constant hazard of death is seen in all oncology indications and all treatments and used this to justify their approach to extrapolation. However, all prior evidence is based on traditional cytotoxic chemotherapy, which did not demonstrate the long-term survival benefit that has been seen with several immuno-oncologics in a range of indications, as outlined below (NICE, 2016b). We believe these data show that the ERG estimates are likely to underestimate OS for nivolumab in this indication. As per our survival model, we expect the mortality rate for patients who survive long-term on immuno-oncologics to return to a rate similar to that of the general population at the same age, and for these patients to die from causes other than lung cancer (Bristol-Myers Squibb, 2016a). Discussions with clinical thought leaders have confirmed that they consider this to be clinically plausible (see appendix 20 of the BMS submission dossier). Further, although CheckMate 003 is indeed a non-comparative study with a small patient population (Gettinger et al., 2015), we maintain the use of CheckMate 003 for the OS extrapolation in the absence of other long term follow up data for immuno-oncologic agents in NSCLC, as described in further detail in a dedicated section below. **Decreasing Hazard Over Time** It must be noted that the ERG's assertion that their evidence shows a constant hazard of death in all oncology indications is based on unpublished data, which we have been unable to validate. We assume however, given the recent advent of immuno-oncology treatments, that the ERG data are based on traditional cytotoxic chemotherapy. We consider that the survival profile of these cytotoxic chemotherapies is fundamentally different to that of immuno-oncology treatments, and therefore it would be inappropriate to transfer these data to nivolumab, both generally and in this indication. In order to support this, we have plotted the cumulative hazard of death over time for NSCLC patients in CheckMate 003 to specifically explore whether it is constant, as the ERG suggests. These data,	Thank you for your comment. The committee considered the comments submitted by the company at ACD consultation stage and also a critique by the ERG. It did not consider that the additional evidence was supportive of a decreasing hazard of death with nivolumab and that the evidence presented by the company was robust enough to support it. For further information please see sections 4.10 to 4.12 of appraisal consultation document (ACD).

Consultee	Comment [sic]	Response
	presented in Figure 1, clearly show that the hazard cannot be assumed as constant; indeed, evidence suggests the hazard of death decreases over time (Bristol-Myers Squibb, 2016b). These data therefore refute the ERG survival extrapolation, which is based on constant hazard of death (NICE, 2016b). As we explore further below, CheckMate 003 provides important long-term data that should not be ignored when assessing the likely long-term impact of nivolumab in patients with NSCLC. Therefore, when considering the long-term costs and benefits of nivolumab, the ERG's survival extrapolation should not be considered, and alternatives explored. *Figure has been presented but not replicated here.* **Evidence for Long-term Survival With Immuno-Oncologics** The cumulative hazard plot from CheckMate 003 (Figure 1) suggests that there will be a proportion of patients who receive treatment with nivolumab who exhibit durable long-term survival benefits (Bristol-Myers Squibb, 2016b). To cross-reference this concept, we have compared this with historical data and data from ongoing studies, not just for nivolumab in NSCLC but for other immuno-oncologic agents for the treatment of other malignancies. As can be seen, durable long-term survival has been observed consistently across immuno-oncologic treatments, across cancer types and across studies. This takes the form of the development of a 'plateau' in Kaplan-Meir survival curves. This survival plateau is exemplified in a pooled analysis of data for ipilimumab in melanoma (Schadendorf et al., 2015), as well as nivolumab study CA209-003, in advanced or recurrent malignancies including lung cancer (Bristol-Myers Squibb, 2015) and advanced melanoma (Figure 2)(Hodi, 2016). Although the curves differ slightly in shape, the general trend of long-term survival over time is seen across therapies and indications. *Figure has been presented but not replicated here.* When ipilimumab was under review by NICE for the treatment of previously untreated, unresectable melanoma, Nelson-Aalen plots were drawn to assess the cumulative hazard rate (Figure 3)(NICE, 2014). This clearly shows that the hazard of death is not constant over time for patients treated with ipilimumab in this indication. This therefore supports our hypothesis that while constant hazards might be seen for traditional cytotoxic chemotherapies, the same is not true for immuno-oncologics. *Figure has been presented but not replicated here.* In the NICE appraisal for pembrolizumab for advanced melanoma not previously treated with ipilimumab, clinical experts stated that pembrolizumab was expected to provide a long-term survival benefit consistent with that shown in the ipilimumab trials (NICE, 2015d). The committee recognised that this expectation was biologically plausible and that there was no evidence to suggest pembrolizumab would differ from ipilimumab in this respect, thus this concept of a long-term survival	

Consultee	Comment [sic]	Response
	benefit with immuno-oncologics was accepted and incorporated into the economic model. Currently the longest median follow-up we have for nivolumab in non-squamous NSCLC from the CheckMate 057 study is 24 months (Borghaei et al., 2016), which may be too early to see the change in curve seen across other indications; notably, the plateau in the melanoma study for ipilimumab was only seen between 2 and 3 years (Schadendorf et al., 2015). Therefore, and similarly to the assumptions in the appraisal for pembrolizumab in melanoma, we anticipate that once the data mature, the same reduction in mortality will be seen for nivolumab in non-squamous NSCLC. **CheckMate 057 24-month Data Cut** Nivolumab has continued to demonstrate improved rates of OS (29%) versus docetaxel (16%) at 24 months follow-up (Borghaei et al., 2016), as was seen at the 18-month data cut (Figure 4). The hazard ratio (HR) for OS for nivolumab versus docetaxel at 24 months was 0.75 (95% confidence interval [CI], 0.63, 0.91) (Borghaei et al., 2016). The minimum survival follow-up in both treatment arms was 24.2 months, and censoring was clustered following the 2-year time point (Borghaei et al., 2016). Notably, the rapid enrolment of trial patients in CheckMate 057 and their resulting similar duration of follow-up, explains the concentration of censoring in the curve at data cutoff (Borghaei et al., 2016). Therefore Kaplan−Meier estimates of survival after 2 years are not fixed and are not likely to represent the actual situation; as described earlier, the curve is expected to shift outwards (as in other indications), as a result of further follow-up in currently censored patients. *Figure has been presented but not replicated here.* It is important to note that [redacted] had crossed over to nivolumab at the time of the 24-month database lock and received [redacted] of nivolumab. Nine of them were still on nivolumab at database lock, representing [redacted] (Borghaei et al., 2016; Bristol-Myers Squibb, 2016d). [redacted]. Therefore, these patients may substantially influence the shape of the curve. In terms of PFS, 12% of patients treated with nivolumab remained in PFS at 24 months, compared with 1% of docetaxel-treated patients. The HR for PFS was 0.89 (95% CI, 0.75, 1.07) for nivolumab versus docetaxel (Figure 5) (Borghaei et al., 2016). *Figure has been presented but not replicated here.* No new responses were observed between the 1- and 2-year data cutoffs (objective response rates [ORRs] were unchanged) (Table 1)(Borghaei et al., 2016). At the 2-year data cutoff, median duration of response was approximately three times longer with nivolumab than with docetaxel.	

Consultee	Comment [sic]	Response
	[redacted] of patients who responded to nivolumab had ongoing responses at the 2-year data cutoff, while [redacted] who responded to docetaxel had ongoing responses. Further, the duration of response with nivolumab may currently be underestimated, due to the censoring (Bristol-Myers Squibb, 2016d). These data suggest that response to nivolumab is long-term, and we anticipate that this trend will continue at the next data cut. The known relationship between response and OS (Blumenthal et al., 2015), suggests that long-term OS will also be seen with nivolumab. *Table has been presented but not replicated here.* **CheckMate 003 Data** As mentioned above, although CheckMate 003 is a non-comparative study with a small patient population (Gettinger et al., 2015), we believe it demonstrates that immuno-oncologic agents can produce an unprecedented long-term response in NSCLC; objective response was observed in 13 (17.6%) patients with non-squamous NSCLC histology specifically (Gettinger et al., 2015). Clinicians that we consulted during submission development considered that it is appropriate to use CheckMate 003 to validate potential long-term survival for patients with non-squamous NSCLC treated with nivolumab (see appendix 20 of the BMS submission dossier), in support of data from CheckMate 057 and survival estimates. Considering the limited available follow-up in CheckMate 057, BMS acknowledges that functional forms fitting with-trial data from CheckMate 003 and 057 are different. However, data from CheckMate 003 do represent a conservative estimate of long-term data for nivolumab. Notably, patients in CheckMate 003 had metastatic NSCLC at trial entry and similar baseline patient characteristics (Table 2) (Gettinger et al., 2015). It is important to note that: • Patients in CheckMate 003 were more heavily pre-treated than, and their median survival (9.9 months) was inferior to that in CheckMate 057 (12.2 months). In addition, OS rates at 6 months (67% versus 66%), 1 year (51% versus 42%), and 2 years (29% versus 24%) were similar or higher for patients in CheckMate 057. • ORR in both studies was similar (19% in CheckMate 057; 17.1% in CheckMate 003), as was median duration of response (DOR; 17.2 months in CheckMate 057; 17 months in CheckMate 003). Of note, the CheckMate 003 cohort with fewer treatment options died more rapidly, allowing the plateau in the OS curve (and apparent difference in shape to CheckMate 057) to become apparent earlier. DOR was similar across studies, and treating patients with IO earlier in the treatment course, as well as the slightly higher ORR rate in CheckMate 057, means that OS at 3 and 4 years in the 057 cohort could be expected to be equal to, or above, that of CheckMate 003, in spite of the apparent difference in shape to date. On this basis, BMS thus believes the extrapolation of OS by the ERG to be clinically implausible. • A comparison of CheckMate 003 with the Kaplan-Meier curve of OS in the ipilimumab registrational trial in advanced melanoma, as well as the pooled analysis, may serve as a second	

Consultee	Comment [sic]	Response
	confirmatory model for what is seen in the CheckMate 057, since the patterns are highly similar. Notably, as seen with ipilimumab, a constant hazard appeared to exist in the first two years; however, this was followed by clear demonstration of decreasing hazards, shifting the shape of the OS curve, with a plateau appearing between 2-3 years and extending onward long-term. We believe the data show that these immuno-oncologic agents can produce a trend towards long-term survival in a proportion of patients, which is unprecedented in NSCLC. *Table has been presented but not replicated here.* Further, the OS curve for nivolumab seen in CheckMate 057 sits above that seen in CheckMate 003, which demonstrates improved survival; however, it follows the same trend. Therefore the CheckMate 003 study supports the concept of long-term survival in immuno-oncologics, and specifically, nivolumab in NSCLC. As such, this casts doubt on the ERG assumption that no long-term benefit exists with nivolumab. We therefore believe that the extrapolation provided below is appropriate, and can be considered a midway point between the ERG and BMS original extrapolations. The incremental cost-effectiveness ratios (ICERs) relating to this extrapolation are provided below. **Conclusion** Although long-term survival is not seen with chemotherapy, evidence exists from trials of immuno-oncology treatments demonstrating that their use can result in long-term survival. Notably, although comparative studies of nivolumab in non-squamous NSCLC are not yet mature, the data are following the same trend as seen in other indications, as well as other immuno-oncology therapies. As such, these data do not support the ERG assumption of constant hazard (which was based on chemotherapeutic agents) and are supportive of long-term benefit, as anticipated by BMS. Therefore the current ERG approach to estimating survival is not a reasonable interpretation of the evidence and alternative approaches should be considered, as outlined below in the section entitled “Presentation of BMS new Base-Case Cost effectiveness Analyses”.	
BMS	**4.7 LONG-TERM OVERALL SURVIVAL EXTRAPOLATION: VALIDATION USING THE CHECKMATE 57 24-MONTH DATA** As described above, data from the 24-month data cut from CheckMate 057 have just become available (Borghaei et al., 2016). Within the time available we have used these data to validate the BMS and ERG survival extrapolations (which used the 12-month and 18-month data cut respectively)(NICE, 2016b). It is clear from Table 3 that the estimate for OS at 2 years using the 24-month data cutoff is in line with the previous estimates. The survival curves proposed by BMS and the ERG have not differentiated by this point (see Figure 6), and therefore the 24-month data does not support one approach over another. It is only from approximately 3 years follow-up that the BMS and ERG OS extrapolations begin to diverge, and therefore if relying on the CheckMate 057 data for validation of approach, at least another year of follow-up is required. The docetaxel curves are very similar using the two extrapolation curves and were not therefore explored.	Thank you for your comment. The Committee considered that the results of the 12 month, 18 month and 24 month data cuts were very similar and that all data could be considered for decision making. It also concluded that nivolumab is clinically effective and offers a gain in survival compared with docetaxel. For further information please see sections 4.10 to 4.12 of the ACD.

Consultee	Comment [sic]	Response
	The estimate for rate of PFS at the 2-year data point is slightly higher using the 24-month cutoff than at previous cutoffs. Thus the data are reinforcing that long-term PFS is possible with nivolumab. The TTD data are also in line with previous estimates. It is anticipated that those patients who are still responding at 2 years will also have strong post-progression survival. *Table and figure has been presented, but not replicated here.*	
BMS	**4.8. COMPARISON WITH NINTEDANIB** The ERG's comparison of nivolumab and nintedanib + docetaxel, used in the economic model was based on the assumption that the docetaxel arms in the two studies (LUME-Lung 1 and CheckMate 057) were reasonably similar, meaning that an unadjusted indirect comparison could be made (NICE, 2016b). In terms of the statistical approach, conducting an unadjusted comparison does not respect the randomisation of the trials, so even if a small (non-statistically significant) difference is observed between the docetaxel arms, which may be important and could affect the extrapolation. Therefore, current guidance does not recommend that unadjusted comparisons are used (Jansen et al., 2011). It is also important to note that there are some key differences between the two studies that place the ERG's assumption into doubt and mean that cross-trial comparisons should be treated with caution (Reck et al., 2014). In particular, there are differences in the proportion of patients each study who were male or current/former smokers (Table 4). In addition, there is an absence of important prognostic information relating to the adenocarcinoma-only subgroup of LUME-Lung 1, namely (Reck et al., 2014): • Stage of disease • CNS metastases (not available for the adenocarcinoma subpopulation) • Best response to most recent prior systemic treatment • Time from completion of most recent systemic treatment. *Table has been presented, but not replicated here* These known differences in baseline characteristics, along with the uncertainty in other characteristics means that we cannot assume the populations in the two studies are the same, and therefore the unadjusted indirect comparison of nivolumab and nintedanib + docetaxel should be treated with caution. Finally, in line with the explanation in the section 'Long-term overall survival benefit of nivolumab' above, it is anticipated that nivolumab will exhibit greater long-term overall survival than traditional chemotherapy. Therefore, as for the comparison with docetaxel, it is inappropriate to fit an exponential to both curves (assuming a constant hazard of death), when long-term survival is likely for nivolumab, which is seen in terms of decreasing hazard of death.	Thank you for your comment. The Committee considered the different methods used for the comparison of nivolumab with nintedanib plus docetaxel and the additional supporting evidence submitted by the company at ACD stage and also a critique by the ERG. It considered that both approaches had limitations, but concluded that the unadjusted indirect comparison by the ERG was more plausible, because it did not assume that the proportional hazard assumption holds. For further information please see section 4.11 of ACD.

Consultee	Comment [sic]	Response
BMS	**4.9 PROGRESSION-FREE SURVIVAL VERSUS TIME TO TREATMENT DISCONTINUATION** As noted in the ACD, in the company submission model, we used time to treatment discontinuation (TTD) rather than progression-free survival (PFS), to model the PFS health state (NICE, 2016a). This was due to the assumption that patients who are treated with nivolumab post-progression continue to receive a clinical benefit. In their review of this model, the ERG suggest that TTD is used to model costs and PFS to model benefits (NICE, 2016b). However, this ignores the benefit that those patients treated post-progression continue to receive from nivolumab. In CheckMate 057, patients in the nivolumab arm could receive nivolumab after progression if they met certain criteria including investigator-assessed clinical benefit and no rapid disease progression; tolerance of study drug and stable performance status (Bristol-Myers Squibb, 2013). This allowance was made in the study protocol due to accumulating evidence that patients may continue to gain benefit because standard response definitions, such as RECIST or WHO, do not provide a complete assessment of immuno-oncologic agents, and might incorrectly suggest initial evidence of progressed disease (PD) (Wolchok et al., 2009). In order for a patient to receive treatment after progression in CheckMate 057, the physician had to feel that a patient continued to achieve clinical benefit from receiving treatment and ensure that there was no deterioration in performance status; treatment was stopped upon any further progression (Bristol-Myers Squibb, 2013). This means that those patients receiving nivolumab post-progression were more akin to the “PFS” health state, than the “PD” one in terms of both costs and outcomes, and were certainly not the equivalent of patients with progressed disease in the van den Hout study, who by definition had PS2 (van den Hout et al., 2006), that the ERG have recommended be used to quantify HRQoL in patients with progressed disease (see 4.11 below)(NICE, 2016b). By using TTD to model both costs and benefits, this difference in the health state of patients treated post-progression is captured in terms of both costs and benefits. Whereas using the ERG approach means that these patients are still accruing all the costs of treatment but are assumed to receive no benefit. We therefore consider that TTD is the most appropriate outcome for modelling the PFS health state.	Thank you for your comment. The Committee considered the additional supporting evidence submitted by the company and also a critique by the ERG on the use of time to treatment discontinuation for modelling progression-free survival. It considered that because continuing treatment after progression is usually determined by clinician and patient discussion, rather than objective criteria, time to treatment discontinuation cannot be considered as a reliable substitute for progression-free survival. For further information please see section 4.12 of ACD.
BMS	**4.11 ASSESSMENT OF UTILITY** Progressed Disease The ERG approach to estimating utility for the PD heath state uses the van den Hout et al. (2006) study, which is representative of the EQ-5D of patients with stage III or IV NSCLC who were treated with palliative radiotherapy for symptomatic relief. In order for this to be appropriate, the health related quality of life of PD patients in CheckMate 057 would have to be equivalent to palliative care patients in the Van den Hout et al. publication. However, the majority of patients in van den Hout et al. (2006) had ECOG performance status (PS) of 2 or more, and patients receiving systemic chemotherapy were excluded (van den Hout et al., 2006).	Thank you for your comment. The Committee considered the revised utility values for the progressed disease health state submitted at ACD consultation stage by the company and the ERG. It considered that the decline in completing the EQ 5D questionnaire during CheckMate 057 might have resulted in

Consultee	Comment [sic]	Response
	Conversely, patients enrolled in the CheckMate 057 study all had a PS0-1 (Borghaei et al., 2015). Further, over half of patients (42% nivolumab; 50% docetaxel) went on to receive a 3rd line systemic treatment following progression (Borghaei et al., 2015); these progressed patients would have had a better prognosis in order to receive such 3rd line systemic treatment, and are thus not reflective of symptomatic patients receiving radiotherapy. Similarly, those patients who continued to receive nivolumab post-progression continued to gain clinical benefits from treatment, but would be considered to be in the PD health state using the ERG approach. Clearly, the health related quality of life of these patients would not be that of a patient with PS2 NSCLC receiving palliative radiotherapy and end-of-life care. As such, the populations in the Van den Hout et al. (2006) study and the CheckMate 057 study cannot be considered equivalent and the use of the van den Hout et al. (2006) estimate of utility for patients with PD is a large under-estimation for the patient population under consideration. Further, NICE have previously accepted the following utilities for PD in recent appraisals: • Nivolumab in squamous NSCLC (TA811): 0.509 (NICE, 2015a) • Nintedanib (TA347): 0.64 (NICE, 2015b) • Erlotinib and gefitinib (TA374): 0.47 (NICE, 2015c) We anticipate that patients in the nivolumab in squamous NSCLC, and nintedanib appraisals are similar to those in the non-squamous NSCLC population, and as such, argue that the utilities applied by the ERG to this population are inappropriate. We thus consider the utilities used by BMS to be more appropriate, as well as in line with the reference case. We accept the appraisal committee's suggestion that a disutility for end-of-life should be applied (NICE, 2016a). However, there are few data around end-of-life utilities in NSCLC, and definitions vary between these. We identified one study by Viganò et al. (1999) where patients spent approximately 4 weeks in a hospice setting (Vigano et al., 1999). We have therefore applied the PD end-of-life health utility from van den Hout et al. (2006) for twice this duration (8 weeks) as a conservative estimate within revised utility calculations presented in our revised base-case presented in the section "Presentation of BMS new Base-Case Cost effectiveness Analyses" below.	selection bias and influenced the utility values, therefore it concluded that the utility value put forward by the company (0.657) was likely to be an overestimation. However it also noted the ERG's utility value was based on a study which had been conducted in a population which was less fit than that in CheckMate-057, therefore it could underestimate the true value. It concluded that a value between 0.657 and 0.48 should be used in the model for the progressed disease health state. For further information please see section 4.15 of ACD.
BMS	**PRESENTATION OF BMS NEW BASE-CASE COST EFFECTIVENESS ANALYSES** BMS has considered the recommendations of the ERG (NICE, 2016b), the findings of the AC (NICE, 2016a) and the newly available 24-month data cut from CheckMate 057 (Borghaei et al., 2016) and provide a new base-case cost-effectiveness analysis below (Bristol-Myers Squibb, 2016a). Updates to the Previous BMS Base-Case Model The BMS model has been updated based on the ERG's review to incorporate appropriate changes, or identify alternative scenarios that address the ERG's concern (Bristol-Myers Squibb, 2016c). The errors that the ERG identified in terms of the costs of nivolumab and applying costs at the start of	Thank you for your comment. The Committee considered the revised cost-effectiveness evidence presented at ACD consultation stage. It considered that since the ICERs for the comparisons between nivolumab and docetaxel or nintedanib plus docetaxel were much higher than

Consultee	Comment [sic]	Response
	each cycle have been corrected. In addition, the following change have been made in line with our responses above: • New long-term survival models based on the 24-month data from CheckMate 057 (see below) • Revised utility value for the PD health state of 0.650. This is a weighted utility, incorporating a disutility to account for end-of-life (0.476), based on van den Hout et al. (2006), into the estimate based on CheckMate 057 data (0.688). In line with our reasoning above, we have utilised TTD to model the PFS health state and our approach to compare nivolumab and nintedanib (Bristol-Myers Squibb, 2016a). **Alternative Extrapolations Based on Hazard Profile** Long-term survival data for new therapies such as immuno-oncologics are only now becoming available. The most appropriate OS extrapolation needs to reflect this emerging evidence and the evidence available to date shows that the hazard for mortality decreases over time. While we strongly disagree with the ERG's specific OS extrapolation (NICE, 2016b), based on the incorrect assumption of a constant hazard past a certain point, we do recognise that hazard profiles provide useful insight into how long-term survival may be modelled. We have reassessed plausible OS extrapolations based on the 24-month data from CheckMate 057 and expected hazard profile over time, and suggest that either the log-normal or log-logistic extrapolations provide a reasonable alternative, based on the ERG's preferred approach but appropriately reflecting the data available for immuno-oncologic agents. In line with BMS' initial submission (NICE, 2016b), a range of survival analyses for both OS and TTD were undertaken and assessed for fit based on AIC/BIC, in line with DSU recommendations (Latimer, 2013). In addition, those factors highlighted by the ERG (patients not surviving longer than the general population and OS and PFS/TTD not crossing)(NICE, 2016b) were assessed when identifying the most valid curves. For both OS and TTD, log-normal was the best fitting curve for both nivolumab and docetaxel in terms of AIC and BIC and all of the other clinical validity checks and we present this as our base-case (Bristol-Myers Squibb, 2016c). As we recognise that the appraisal committee felt our extrapolation was too optimistic and we have shown the ERG approach to be too conservative (NICE, 2016a), we identified other extrapolations that meet the clinical validity criteria while acknowledging this concern. Of these, the most plausible scenario was the use of generalised gamma for OS and log-normal for TTD. Although the ERG criticised the use of a generalised gamma survival model when based on the 12-month data cut (NICE, 2016b), this new extrapolation, based on the 24-month data cut does not have the same validity issues and provides a valid alternative scenario, in between the BMS base-case and ERG approach. The OS extrapolations for nivolumab are presented in Figure 7, for the 24-month data cut; this includes the best fitting curves (log-normal and generalised gamma) as well as the exponential	could be considered a cost-effective use of NHS resources, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life, it could not recommend nivolumab for treating non-squamous NSCLC. For further information please see sections 4.17 to 4.19 of the ACD.

Consultee	Comment [sic]	Response

(Bristol-Myers Squibb, 2016c). It also includes the ERG curve using the 18 month data and the generalised gamma curve from BMS' original submission, which was based on the 12-month data (NICE, 2016b).

Figure has been presented but not replicated here.

Summary Results at List Price

Based on the model revisions outlined, results are presented in Table 5 for both the base-case (log-normal for both OS and TTD) and the alternative scenario (generalised gamma for OS, log-normal for TTD (Bristol-Myers Squibb, 2016c). These results assume the costs of nivolumab at list price.

Table 5. Results of the Revised Cost-effectiveness Model Using 24-month Data, Nivolumab at List Price

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Base-case (log-normal for both OS and TTD)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel				52,206	[redacted]	0.49	106,653
Nintedanib plus docetaxel				38,549		0.22	177,698
Alternative scenario (generalised gamma for OS, log-normal for TTD)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel				51,657	[redacted]	0.45	114,235
Nintedanib plus docetaxel				38,855		0.24	163,798

Source: Bristol-Myers Squibb (2016c)

Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was conducted using a second-order Monte Carlo simulation run for 1,000 iterations, using the parameters outlined in our original submission. Results of the PSA for the base-case are shown below for both the BMS base case and alternative scenario (Bristol-Myers Squibb, 2016c).

BMS base case model

Table 6. Results of Probabilistic Sensitivity Analysis: BMS base case

Technology	Total costs (£)	Total QALYs	Incremental	Incremental	ICER (£)

Consultee	Comment [sic]	Response

			costs (£)	QALYs	incremental (QALYs)
Probablistic values					
Nivolumab	[redacted]	[redacted]	52,834	0.48	110,658
Docetaxel					
Nintedanib plus docetaxel			38,814	0.21	182,189
Deterministic values					
Docetaxel			52,206	0.49	106,653
Nintedanib plus docetaxel			38,549	0.22	177,698

Figures have been presented, but not replicated here.

A one-way sensitivity analysis was undertaken by varying cost, utility and OS base-case parameter values by their CIs (where available) or ±20% in line with the approach in our original submission, results are presented below (Bristol-Myers Squibb, 2016c).

Tables and figures have been presented, but not replicated here.

BMS alternative scenario

Table 9. Results of Probabilistic Sensitivity Analysis: BMS Alternative Scenario

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Probablistic values					
Nivolumab	[redacted]	[redacted]	52,539	0.47	112,538
Docetaxel					
Nintedanib plus docetaxel			39,294	0.26	152,635
Deterministic values					
Docetaxel			51,657	0.45	114,235
Nintedanib plus docetaxel			38,855	0.24	163,798

Tables and figures have been presented, but not replicated here.

BMS	**CONCLUDING REMARKS** Nivolumab is an innovative treatment option that offers a survival and HRQoL benefit as well as	Comment noted.

Consultee	Comment [sic]	Response
	reduced toxicity to patients with non-squamous NSCLC who have received prior therapy. This represents a remarkable further advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. In consideration of the proposed PAS (results provided in Appendix), Nivolumab is a cost effective treatment option for patients with non-squamous NSCLC who have received prior therapy.	
Roy Castle Lung Cancer Foundation (RCLCF)	• We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Nivolumab in this indication. • We welcome many of the conclusions reached by the Appraisal Committee in this ACD o Nivolumab is a clinically effective treatment option for previously treated non squamous non small cell lung cancer, compared with Docetaxel, Docetaxel/Nintedanib and Best Supportive Care (section 4.3, 4.4) o Nivolumab is an innovative therapy (section 4.17) o Nivolumab meets the criteria of a life extending, end of life treatment (section 4.16) • We note that the Appraisal Committee has reached this negative decision, based on cost issues - Nivolumab, having not been deemed a cost effective use of NHS resources. (section 4.19). We note the Appraisal Committee's conclusion that the "most plausible incremental cost-effectiveness ration for Nivolumab, compared with Docetaxel is £91,100 per quality adjusted life year gained". And the "most plausible ICER for Nivolumab, compared with Docetaxel and Nintedanib is £93,400 per quality adjusted life year gained" (section 4.12 and 4.13) • **On behalf of the many lung cancer patients who would derive benefit from this therapy, we strongly urge dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues are addressed.** Advanced Lung cancer remains a devastating disease for many. We hope that compromise and agreement on price can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	Thank you for your comment. The Committee considered the symptoms of NSCLC and their impact on patients and their families. It also revised cost-effectiveness evidence presented by the company and by the ERG at ACD stage. The ICERs for the comparisons between nivolumab and docetaxel or nintedanib plus docetaxel were much higher than could be considered a cost-effective use of NHS resources, therefore it could not recommend nivolumab for treating non-squamous NSCLC. For further details please see sections 4.1, 4.2 and 4.17 to 4.19 of the ACD.
National Lung Cancer Forum for Nurses (NLCFC)	NLCFN emphasised that there is a high unmet need for this patient group since current treatment options are limited and many patients are unable to tolerate the side effects of current treatments. Relapsed non-squamous NSCLC has debilitating and distressing symptoms, therefore improving quality of life and even a small extension to life would and should be considered as a significant	Thank you for your comment. The Committee considered the symptoms of NSCLC and their impact on patients and their

Consultee	Comment [sic]	Response
	benefit by both patients and their families.	families. For further details please see sections 4.1 and 4.2 of ACD.
National Cancer Research Institute (NCRI)- Association of Cancer Physicians (ACP)- Royal College of Physicians (RCP)- Royal College of Radiologists (RCR)	We note that NICE have taken due consideration that nivolumab is an innovative treatment which gives a survival advantage and, therefore, feel there will be little ground for appeal. We understand the importance of cost effectiveness and would support any moves by either the drug companies involved or NICE to ensure all avenues are explored to ensure innovative treatments are available for patients. I would be grateful if you could confirm receipt.	Thank you for your comment. The Committee considered the symptoms of NSCLC and their impact on patients and their families. It also revised cost-effectiveness evidence presented by the company and by the ERG at ACD stage. The ICERs for the comparisons between nivolumab and docetaxel or nintedanib plus docetaxel were much higher than could be considered a cost-effective use of NHS resources, therefore it could not recommend nivolumab for treating non-squamous NSCLC. For further details please see sections 4.1, 4.2 and 4.17 to 4.19 of the ACD.

Comments received from commentators

Commentator	Comment [sic]	Response
Boehringer Ingelheim	Has all of the relevant evidence been taken into account? 1. Nivolumab European Public Assessment Report (EPAR), EMA/246304/2016, dated 25 February 2016, and updated summary of product characteristics (SmPC) contain new, partly previously unpublished results, and the following conclusions: a. Early death rates (i.e. within 3 months): The EPAR notes (pages 36-37, Figure 11) “The docetaxel group shows a similar death rate across the different baseline groups according to baseline PD-L1 expression. The additional post hoc analyses revealed that for nivolumab patients with a baseline PD-L1 expression <10%, the early death rate was around 25%; this death rate is higher than for docetaxel. In contrast, patients with a PD-L1 expression ≥ 50% nivolumab show a low overall early death rate (6.8%, which is lower than observed with docetaxel 24%).” It concludes that	Thank you for your comment. The Committee considered whether a subgroup of patients based on the level of PD-L1 expression can be identified and whether nivolumab works more effectively in this subgroup. However, the company for nivolumab had not presented any further evidence of the clinical effects of the treatment in different subgroups of people according to the level of PD-L1 expression. For further information please see section 4.8 of the ACD.

Commentator	Comment [sic]	Response
	"Therefore, it is cannot be ruled out that the baseline PD-L1 expression percentage may affect the early death rate." b. The EPAR also notes that "Regarding OS benefit and other key efficacy results according to baseline PD-L1 status, it is noted that results in PD-L1 negative/non-quantifiable patients are similar to those seen in the docetaxel patients, with practically no differences between this subset of patients and those in the docetaxel group, with numerically more deaths in nivolumab patients than docetaxel during the first 6 months of treatment." 2. The Checkmate-057 publication (Borghaei, 2015) Supplementary Appendix reports: a. Significant interaction P-values of PD-L1 expression for both PFS and OS (figure S7) indicating a strong effect modification by PD-L1 levels. b. Kaplan Meier curves for PFS (figure S8A) and OS (figure S8B) at the 1%, 5% and 10% PD-L1 Expression Levels, showing a the influence of the PD-L1 cut-off used on the crossing of the curves. This could lead to potential alternative solutions to the currisng OS curves issue discussed in the comment #3 below. 3. Alternative causality and solutions for the crossing OS curves a. The manufacturer's submission mentions the issue of the "crossing of the OS curves" (page 150-151 of the manufacturer's submission, Figure 28), however only suggests "pseudo-progression" as a possible cause for this. We support the ERG in its statement "The ERG is not convinced that the data presented support this claim" and that "a number of theories exist for this delay, and the exact underlying mechanism is unclear" (pages 11 and 36, respectively, of the ERG submission). b. The additional information in the EPAR and SmPC (#1 above) might form a plausible alternative explanation where early deaths in patients with low PD-L1 expression might help explain the crossing curves. It could therefore be important to consider the OS curves for different PD-L1 cut-off levels in trying to solve the issue of the crossing curves. 4. While we understand that considering the post-hoc nature of these analyses and the limited size of some of the subgroups and that these results need to be taken with caution, these additional points could be considered in this	

Commentator	Comment [sic]	Response
	assessment, especially as the highest benefits of nivolumab appear to be observed at PD-L1 cut-off of 50%.	
Boehringer Ingelheim	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 5. ACD Section 4.3: In view of our comments #1-4 above (new data in the EPAR, SmPC, as well as existing data in the Supplementary Appendix of the Checkmate-057 publication (Borghaei, 2015), the conclusions about clinical benefits in survival may have to be reconsidered based on the PD-L1 expression levels; as well as the data on the early mortality. 6. ACD section 4.4: While the committee accepted that the indirect treatment comparison "was not a reliable estimate of comparative effectiveness", it goes on to conclude a gain in quality of life with nivolumab based on avoidance of toxicities associated with docetaxel based on clinical and patient expert comments. However, based on the early mortality data and the PD-L1 cut-off (our comments #1-4 above), the subgroups of patients with ≤50% PD-L1 expression could be considered to have better overall survival with docetaxel than nivolumab and therefore accrue higher QALYs with docetaxel than with nivolumab. 7. ACD section 4.5: We support the committee's conclusion that "it could be plausible that nivolumab might have a different level of clinical effectiveness according to PD-L1 expression." The current clinical or cost-effectiveness estimates do not however take this into account, even though this in itself might help to explain and solve the crossing OS curves (by accounting for the increased early mortality by PD-L1 expression levels, and accounting for differential efficacy of nivolumab vs docetaxel based again on PD-L1 expression levels). 8. ACD sections 4.6-4.9: In modelling OS for comparing nivolumab to both docetaxel and nintedanib + docetaxel, "the proportional hazards assumption was not met", primarily due to the crossing curves. The solution adopted by the ERG was to use 18-month data and an exponential extrapolation. However, given our comments # 1-4 above, we'd suggest that PD-L1 expression level was a key effect modifier, and therefore should be used to model survival outcomes.	Thank you for your comment. The Committee considered whether a subgroup of patients based on the level of PD-L1 expression can be identified and whether nivolumab works more effectively in this subgroup. However, the company for nivolumab had not presented any further evidence of the clinical effects of the treatment in different subgroups of people according to the level of PD-L1 expression. It concluded that, whilst it could be plausible that nivolumab might have a different level of clinical effectiveness according to the level of PD-L1 expression, it had not been presented with any additional evidence to consider these subgroups separately. For further information please see section 4.8 of the ACD.

Commentator	Comment [sic]	Response
	9. ACD Section 4.13 and 'Summary of appraisal committee's key conclusions', box 'key conclusions': The fourth (of five) bullet points currently states "The most plausible ICER for nivolumab compared with nintedanib plus docetaxel was £93,400 per QALY gained". While the text in section 4.13 clarifies that this figure does not include the existing PAS for nintedanib (and that including this would make the most likely ICER to be much higher), the summary table omits this clarification. For increased clarity, we would propose the statement in the summary table to also reflect this fact that the ICER quoted does not account for the PAS for nintedanib and is therefore an underestimation.	
Boehringer Ingelheim	Are the recommendations sound and a suitable basis for guidance to the NHS? 10. While we support the recommendations in the ACD, we would propose that a stronger case exits with recent and existing data on early mortality and effect of PD-L1 expression on treatment effect to make any reconsideration of the recommendation contingent on the PD-L1 cut-off levels.	Thank you for your comment. The Committee considered whether a subgroup of patients based on the level of PD-L1 expression can be identified and whether nivolumab works more effectively in this subgroup. However, the company for nivolumab had not presented any further evidence of the clinical effects of the treatment in different subgroups of people according to the level of PD-L1 expression. For further information please see section 4.8 of the ACD.
Boehringer Ingelheim	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? 11. Not to our knowledge at this point.	Comment noted.

Summary of comments received from members of the public

Theme	Response
Nivolumab is a new and innovative treatment, which is indicated by its EAMS designation.	Thank you for your comment. The Committee considered the innovative nature of this new technology and concluded that nivolumab is innovative, but there were no additional benefits in health-related quality of life that had not been already captured in the QALY calculations. For further information please see section 4.17 of the ACD.
Non-squamous non-small-cell lung cancer is a devastating disease with limited treatment options currently available and high unmet medical need.	Thank you for your comment. The Committee considered the implications of NSCLC on patients and their families and the current clinical management of the disease. For further information please see sections 4.1 and 4.2 of ACD.
Nivolumab is a more tolerable option with better adverse events profile and less toxicity, compared to the current standard of care.	Thank you for your comment. The Committee considered the adverse event profile of nivolumab and the clinical management of NSCLC. For further information please see sections 2 and 4.2 of ACD.
Nivolumab seems to be more effective in a subgroup of patients with higher level of PD-L1 expression.	Thank you for your comment. The Committee considered whether a subgroup of patients based on the level of PD-L1 expression can be identified and whether nivolumab works more effectively in this subgroup. However, the company for nivolumab had not presented any further evidence of the clinical effects of the treatment in different subgroups of people according to the level of PD-L1 expression. For further information please see section 4.8 of the ACD.

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]

Bristol-Myers Squibb Pharmaceuticals Ltd Response to the Appraisal Consultation Document

Friday 3rd June 2016

EXECUTIVE SUMMARY

In the Appraisal Consultation Document (ACD) issued by NICE, nivolumab is not recommended for treating locally advanced non-squamous NSCLC in adults whose disease has progressed after chemotherapy (NICE, 2016a). Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) disagrees with the proposed recommendation for nivolumab in previously treated locally advanced or metastatic non-squamous NSCLC and provides its comments by section of the ACD below, with a focus on whether the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence and whether the provisional recommendations are a sound and suitable basis for guidance to the NHS. In addition, data from the 24-month data cut of CheckMate 057 are now available (Borghaei et al., 2016) and presented below, including revised cost-effectiveness data based on the 24-month clinical outcomes. Finally, a revised patient access scheme (PAS) has been submitted and the cost-effectiveness results including the PAS are presented in a separate Appendix.

The committee acknowledged that despite recent advances in treatments, the prognosis in terms of survival in NSCLC has not substantially improved in the last 30 years (Cancer Research UK, 2015) and recognised that there is need for effective treatment, which are not associated with high toxicity. In addition, the committee consider nivolumab to be an innovative treatment and a step-change in managing non-squamous NSCLC due to its novel mechanism of action, which is associated with fewer toxicities than the currently available treatment options; docetaxel and nintedanib plus docetaxel. The committee also acknowledged that BMS made nivolumab available via an Early Access to Medicines Scheme (EAMS) (NICE, 2016a); approximately 99 patients receiving treatment via EAMS.

The following key areas are those in which BMS believe the summaries of clinical and cost-effectiveness are not reasonable interpretations of the evidence, and thus the appraisal committee's recommendations are not sound.

Long-term overall survival benefit of nivolumab. The appraisal committee has accepted the evidence review group (ERG) assumption that hazards for overall survival (OS) are constant after an initial treatment period in all oncology indications and treatments (NICE, 2016a). However, evidence shows that for immuno-oncologics, long-term survival is possible, and that while an assumption of constant hazards might be reasonable for chemotherapy, it is unclear that this would apply in the same way for immuno-oncologics (NICE, 2016b). In particular, it is important to note that:

- Decreasing hazards are seen over time (as demonstrated in NSCLC patients in CheckMate 003 – Figure 1), suggesting that some long-term survivors will die of natural causes, rather than NSCLC (Bristol-Myers Squibb, 2016a); long-term survival has been observed with immuno-oncologics in a variety of therapeutic settings, including melanoma (treated with ipilimumab, nivolumab or pembrolizumab) and NSCLC (for nivolumab)(Figure 2 and Figure 3)(Bristol-Myers

Squibb, 2015; Hodi, 2016; Schadendorf et al., 2015), demonstrated by the development of a 'plateau' in Kaplan-Meir survival curves. Currently the longest median follow-up we have for nivolumab in non-squamous NSCLC from the CheckMate 057 study is 24 months(Borghaei et al., 2016), which may be too early to see the change in curve seen across other indications. Therefore, and similarly to the assumptions in the appraisal for pembrolizumab in melanoma, we anticipate that once the data mature, the same reduction in mortality will be seen for nivolumab in non-squamous NSCLC.

- We maintain that CheckMate 003 supports the assumption that long-term survival can occur in patients with advanced NSCLC treated with nivolumab, considering the similar trends in OS for nivolumab in CheckMate 057 and CheckMate 003 (Bristol-Myers Squibb, 2016b). Paying no consideration to the CheckMate 003 study is unreasonable since it provides the longest follow-up data available to date and shows a notably similar trend in OS for nivolumab when compared with CheckMate 057. Further, patients in CheckMate 003 had metastatic NSCLC at trial entry and similar baseline patient characteristics to patients in CheckMate 057 and ORR in the two studies was similar, as was median duration of response (DOR). For a number of reasons (described in detail below), OS at 3 and 4 years in the CheckMate 057 cohort could be expected to be equal to, or above, that of CheckMate 003.
- New 24-month data from CheckMate 057 continue to support the possibility of long-term survival (Borghaei et al., 2016). Validation of the survival analyses in the BMS base-case and the ERG's approach against the 24-month data shows that the data are still consistent in line with the previous extrapolations (Figure 6)(Bristol-Myers Squibb, 2016a).

The Appraisal Committee's acceptance of the ERG approach to survival extrapolation is not a reasonable interpretation of the available clinical evidence and clinical expert opinion (NICE, 2016a). Therefore, we request that the Committee considers alternative extrapolations which capture the long-term benefit of nivolumab.

Comparison with nintedanib + docetaxel. The ERG conducted an unadjusted comparison between nivolumab and nintedanib on the assumption that the docetaxel arms of the two studies are comparable (NICE, 2016b). However, conducting an unadjusted comparison does not respect the randomisation of the trials and therefore goes against current recommendations. In addition, comparing the baseline characteristics of the docetaxel arms in the two studies shows that there are differences in the patient populations which invalidate the ERG's unadjusted comparison (Borghaei et al., 2015; Reck et al., 2014). We therefore consider that our adjusted approach is more appropriate.

Use of progression-free survival (PFS) and time to treatment discontinuation (TTD) to model the PFS health state. In the BMS base-case, TTD was used to model the PFS health state due to the assumption that patients who are treated with nivolumab post-progression continue to receive a clinical benefit (Bristol-Myers Squibb, 2016a). The ERG

criticised this and said that PFS should be used to model outcomes and TTD to model costs. We reiterate the evidence that patients on nivolumab continue to gain benefit when treated beyond progression and contend that applying a low utility (for progressed disease) to these patients is not appropriate in the light of available data.

Assessment of utility. The Appraisal Committee has accepted the ERG's use of the van den Hout et al. (2006) study to calculate utilities for the progressed disease (PD) health state (0.476)(NICE, 2016a). We argue that the patient population in van den Hout et al. (patients with stage III or IV NSCLC, PS2 treated with palliative radiotherapy) is not the same as that in CheckMate 057 and highlight the utility for PD accepted in the nivolumab squamous NSCLC appraisal [redacted](NICE, 2015a), in the recent nintedanib in NSCLC appraisal (0.64)(NICE, 2015b) and in the erlotinib and gefitinib in NSCLC appraisal (0.47 independent of treatment)(NICE, 2015c) and argue that those accepted in the reviews of nivolumab in squamous NSCLC and nintedanib are likely to be more appropriate than the current committee preferred ERG estimate. In order to ensure the impact of end-of-life is included in the utility estimates, a disutility can be applied to the utility seen in CheckMate 057, based on that from van den Hout (2006), and applied only to the last stage of PD.

Revised cost-effectiveness analysis based on 24-month data from CheckMate 057. BMS has considered the recommendations of the ERG, the findings of the Appraisal Committee and the newly available 24-month data cut from CheckMate 057 and we have provided a new base-case cost-effectiveness analysis (Bristol-Myers Squibb, 2016c). Changes proposed by the ERG including minor corrections have been incorporated and other changes have been made in line with our response to specific ERG and appraisal committee concerns. This includes new long-term survival extrapolations based on the 24-month CheckMate 057 data and a revised utility in the PFS health state that incorporates a disutility for end-of-life (Bristol-Myers Squibb, 2016c).

With the revised model, the ICER using the BMS base case OS extrapolation is £107,000 vs docetaxel and £178,000 vs nintedanib + docetaxel. Deterministic sensitivity analysis revealed that in the comparison with docetaxel, the model was most sensitive to the average body weight and discount rates; in the comparison with nintedanib, the hazard ratio for OS had the greatest impact.

Concluding remarks

Nivolumab is an innovative treatment option that offers a survival and HRQoL benefit as well as reduced toxicity to patients with non-squamous NSCLC who have received prior therapy. This represents a remarkable further advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. In consideration of the proposed PAS (results provided in Appendix), Nivolumab is a cost effective treatment option for patients with non-squamous NSCLC who have received prior therapy.

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2.1 EARLY ACCESS TO MEDICINES SCHEME

As set out in the ACD, nivolumab has been available for the treatment of NSCLC through an EAMS. To date, 284 applications have been made through the EAMS process for nivolumab in PD-L1 mutation positive non-squamous NSCLC; of these, 99 have received treatment with nivolumab.

4.3 AND 4.7 LONG TERM OVERALL SURVIVAL BENEFIT OF NIVOLUMAB

While the appraisal committee recognised some long-term overall survival benefit from nivolumab they were not persuaded that the trial data supported a decrease in the rate of mortality with nivolumab to the extent suggested by our survival extrapolation (see 4.7 below)(NICE, 2016a). They also considered that CheckMate-003 did not support this comparative advantage of nivolumab over docetaxel. The committee therefore concluded that the ERG's approach to extrapolation (applying an exponential curve that assumed a constant hazard of death from 12 months) was more appropriate (NICE, 2016a).

The evidence review group (ERG) have argued that they have (unpublished) evidence that shows that a constant hazard of death is seen in all oncology indications and all treatments and used this to justify their approach to extrapolation. However, all prior evidence is based on traditional cytotoxic chemotherapy, which did not demonstrate the long-term survival benefit that has been seen with several immuno-oncologics in a range of indications, as outlined below (NICE, 2016b). We believe these data show that the ERG estimates are likely to underestimate OS for nivolumab in this indication. As per our survival model, we expect the mortality rate for patients who survive long-term on immuno-oncologics to return to a rate similar to that of the general population at the same age, and for these patients to die from causes other than lung cancer (Bristol-Myers Squibb, 2016a). Discussions with clinical thought leaders have confirmed that they consider this to be clinically plausible (see appendix 20 of the BMS submission dossier).

Further, although CheckMate 003 is indeed a non-comparative study with a small patient population (Gettinger et al., 2015), we maintain the use of CheckMate 003 for the OS extrapolation in the absence of other long term follow up data for immuno-oncologic agents in NSCLC, as described in further detail in a dedicated section below.

Decreasing Hazard Over Time

It must be noted that the ERG's assertion that their evidence shows a constant hazard of death in all oncology indications is based on unpublished data, which we have been unable to validate. We assume however, given the recent advent of immuno-oncology treatments,

that the ERG data are based on traditional cytotoxic chemotherapy. We consider that the survival profile of these cytotoxic chemotherapies is fundamentally different to that of immuno-oncology treatments, and therefore it would be inappropriate to transfer these data to nivolumab, both generally and in this indication.

In order to support this, we have plotted the cumulative hazard of death over time for NSCLC patients in CheckMate 003 to specifically explore whether it is constant, as the ERG suggests. These data, presented in Figure 1, clearly show that the hazard cannot be assumed as constant; indeed, evidence suggests the hazard of death decreases over time (Bristol-Myers Squibb, 2016b). These data therefore refute the ERG survival extrapolation, which is based on constant hazard of death (NICE, 2016b). As we explore further below, CheckMate 003 provides important long-term data that should not be ignored when assessing the likely long-term impact of nivolumab in patients with NSCLC. Therefore, when considering the long-term costs and benefits of nivolumab, the ERG's survival extrapolation should not be considered, and alternatives explored.

Figure 1. Nelson-Aalen Cumulative Hazards Plot, Patients With NSCLC From CheckMate 003

Source: Bristol-Myers Squibb (2016b). Note: this figure is commercial in confidence

Evidence for Long-term Survival With Immuno-Oncologics

The cumulative hazard plot from CheckMate 003 (Figure 1) suggests that there will be a proportion of patients who receive treatment with nivolumab who exhibit durable long-term survival benefits (Bristol-Myers Squibb, 2016b). To cross-reference this concept, we have compared this with historical data and data from ongoing studies, not just for nivolumab in NSCLC but for other immuno-oncologic agents for the treatment of other malignancies.

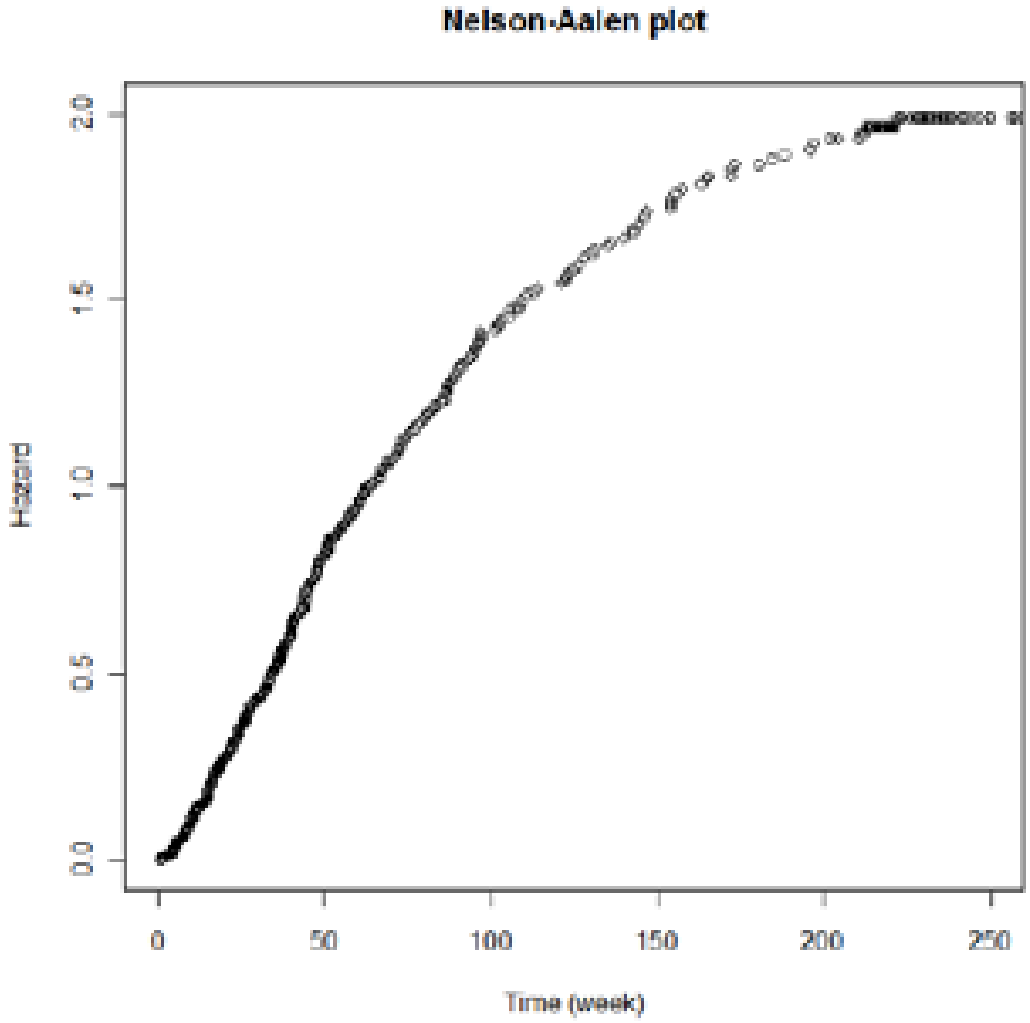
As can be seen, durable long-term survival has been observed consistently across immuno-oncologic treatments, across cancer types and across studies. This takes the form of the development of a 'plateau' in Kaplan-Meir survival curves. This survival plateau is exemplified in a pooled analysis of data for ipilimumab in melanoma (Schadendorf et al., 2015), as well as nivolumab study CA209-003, in advanced or recurrent malignancies including lung cancer (Bristol-Myers Squibb, 2015) and advanced melanoma (Figure 2)(Hodi, 2016). Although the curves differ slightly in shape, the general trend of long-term survival over time is seen across therapies and indications.

Figure 2. Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients With Advanced Melanoma and NSCLC

Sources: Bristol-Myers Squibb (2015); Hodi (2016); Schadendorf et al. (2015). Note: this figure is academic in confidence

When ipilimumab was under review by NICE for the treatment of previously untreated, unresectable melanoma, Nelson-Aalen plots were drawn to assess the cumulative hazard rate (Figure 3)(NICE, 2014). This clearly shows that the hazard of death is not constant over time for patients treated with ipilimumab in this indication. This therefore supports our hypothesis that while constant hazards might be seen for traditional cytotoxic chemotherapies, the same is not true for immuno-oncologics.

Figure 3. Nelson-Aalen Plot From Study CA184-024 of Ipilimumab in Previously Untreated Melanoma



Source: NICE (2014)

In the NICE appraisal for pembrolizumab for advanced melanoma not previously treated with ipilimumab, clinical experts stated that pembrolizumab was expected to provide a long-term survival benefit consistent with that shown in the ipilimumab trials (NICE,

2015d). The committee recognised that this expectation was biologically plausible and that there was no evidence to suggest pembrolizumab would differ from ipilimumab in this respect, thus this concept of a long-term survival benefit with immuno-oncologics was accepted and incorporated into the economic model.

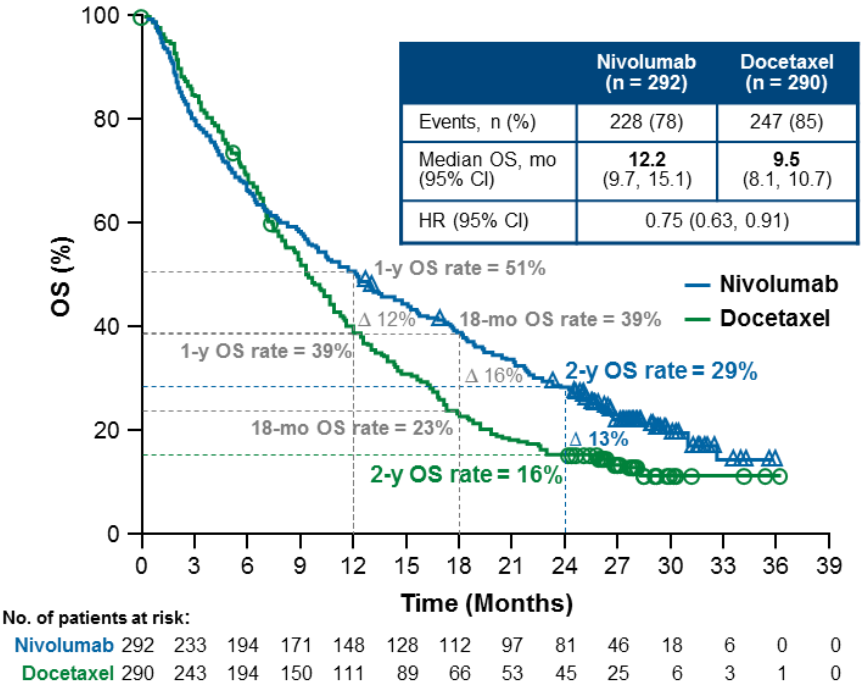
Currently the longest median follow-up we have for nivolumab in non-squamous NSCLC from the CheckMate 057 study is 24 months (Borghaei et al., 2016), which may be too early to see the change in curve seen across other indications; notably, the plateau in the melanoma study for ipilimumab was only seen between 2 and 3 years (Schadendorf et al., 2015). Therefore, and similarly to the assumptions in the appraisal for pembrolizumab in melanoma, we anticipate that once the data mature, the same reduction in mortality will be seen for nivolumab in non-squamous NSCLC.

CheckMate 057 24-month Data Cut

Nivolumab has continued to demonstrate improved rates of OS (29%) versus docetaxel (16%) at 24 months follow-up (Borghaei et al., 2016), as was seen at the 18-month data cut (Figure 4). The hazard ratio (HR) for OS for nivolumab versus docetaxel at 24 months was 0.75 (95% confidence interval [CI], 0.63, 0.91) (Borghaei et al., 2016).

The minimum survival follow-up in both treatment arms was 24.2 months, and censoring was clustered following the 2-year time point (Borghaei et al., 2016). Notably, the rapid enrolment of trial patients in CheckMate 057 and their resulting similar duration of follow-up, explains the concentration of censoring in the curve at data cutoff (Borghaei et al., 2016). Therefore Kaplan−Meier estimates of survival after 2 years are not fixed and are not likely to represent the actual situation; as described earlier, the curve is expected to shift outwards (as in other indications), as a result of further follow-up in currently censored patients.

Figure 4. Overall Survival at the 24-month Data Cut in CheckMate 057



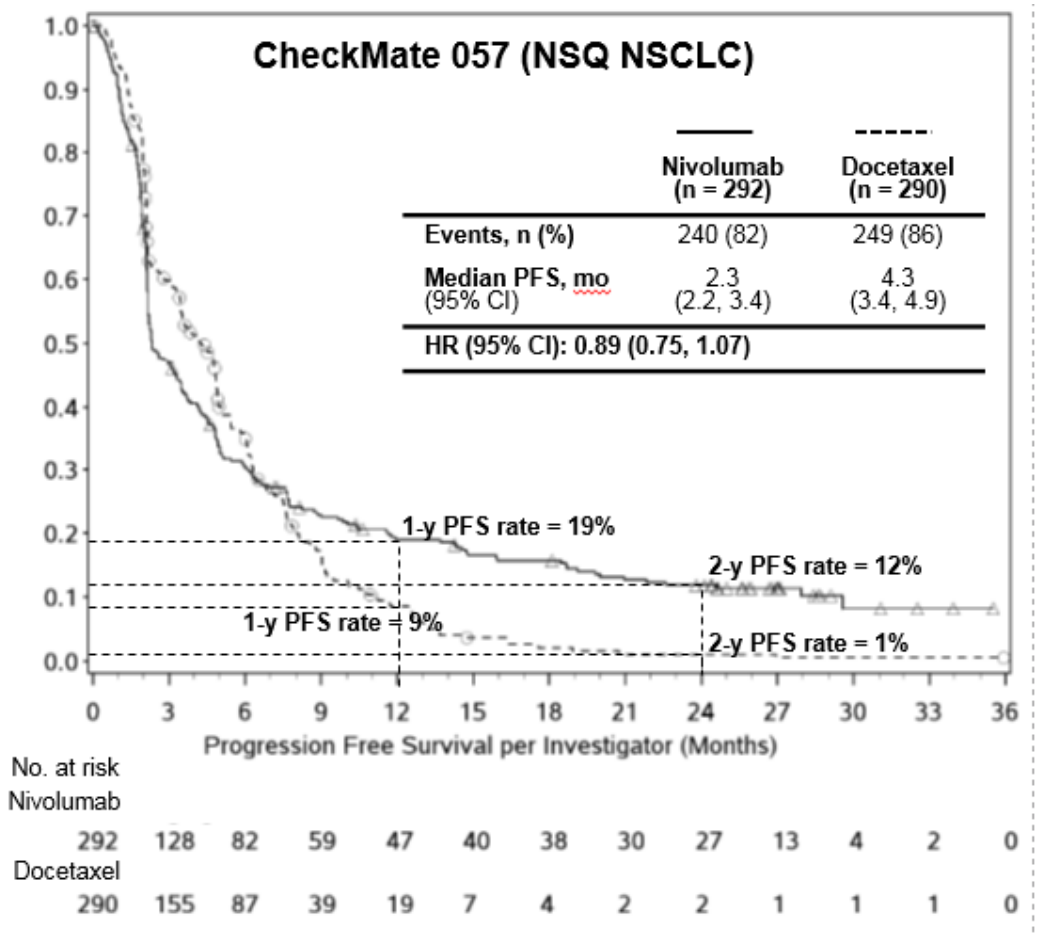
Source: Borghaei et al. (2016)

It is important to note that [redacted] had crossed over to nivolumab at the time of the 24-month database lock and received [redacted] of nivolumab. Nine of them were still on nivolumab at database lock, representing [redacted] (Borghaei et al., 2016; Bristol-Myers Squibb, 2016d). [redacted]

[redacted] Therefore, these patients may substantially influence the shape of the curve.

In terms of PFS, 12% of patients treated with nivolumab remained in PFS at 24 months, compared with 1% of docetaxel-treated patients. The HR for PFS was 0.89 (95% CI, 0.75, 1.07) for nivolumab versus docetaxel (Figure 5) (Borghaei et al., 2016).

Figure 5. Progression-Free Survival at the 24-month Data Cut in CheckMate 057



Source: Borghaei et al. (2016)

No new responses were observed between the 1- and 2-year data cutoffs (objective response rates [ORRs] were unchanged) (Table 1)(Borghaei et al., 2016). At the 2-year data cutoff, median duration of response was approximately three times longer with nivolumab than with docetaxel. [redacted] of patients who responded to nivolumab had ongoing responses at the 2-year data cutoff, while [redacted] who responded to docetaxel had ongoing responses. Further, the duration of response with nivolumab may currently be underestimated, due to the censoring (Bristol-Myers Squibb, 2016d). These data suggest that response to nivolumab is long-term, and we anticipate that this trend will continue at the next data cut. The known relationship between response and OS (Blumenthal et al., 2015), suggests that long-term OS will also be seen with nivolumab.

Table 1. Objective Response Rate at the 24-month Data Cut in CheckMate 057

	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR[a], % (95% CI)	[redacted]	[redacted]
Best overall response, %		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]
Median duration of response,[b] months (Range)	[redacted]	[redacted]
Median time to response,[b] months (Range)	[redacted]	[redacted]
Ongoing response,[b] % (No. ongoing/total responders)	[redacted]	[redacted]

[a]Investigator-assessed; [b]In patients with confirmed responses; + = censored value

Source: Bristol-Myers Squibb (2016d).

CheckMate 003 Data

As mentioned above, although CheckMate 003 is a non-comparative study with a small patient population (Gettinger et al., 2015), we believe it demonstrates that immuno-oncologic agents can produce an unprecedented long-term response in NSCLC; objective response was observed in 13 (17.6%) patients with non-squamous NSCLC histology specifically (Gettinger et al., 2015). Clinicians that we consulted during submission development considered that it is appropriate to use CheckMate 003 to validate potential long-term survival for patients with non-squamous NSCLC treated with nivolumab (see appendix 20 of the BMS submission dossier), in support of data from CheckMate 057 and survival estimates.

Considering the limited available follow-up in CheckMate 057, BMS acknowledges that functional forms fitting with-trial data from CheckMate 003 and 057 are different. However, data from CheckMate 003 do represent a conservative estimate of long-term data for nivolumab. Notably, patients in CheckMate 003 had metastatic NSCLC at trial entry and similar baseline patient characteristics (Table 2) (Gettinger et al., 2015). It is important to note that:

- Patients in CheckMate 003 were more heavily pre-treated than, and their median survival (9.9 months) was inferior to that in CheckMate 057 (12.2 months). In

addition, OS rates at 6 months (67% versus 66%), 1 year (51% versus 42%), and 2 years (29% versus 24%) were similar or higher for patients in CheckMate 057.

- ORR in both studies was similar (19% in CheckMate 057; 17.1% in CheckMate 003), as was median duration of response (DOR; 17.2 months in CheckMate 057; 17 months in CheckMate 003). Of note, the CheckMate 003 cohort with fewer treatment options died more rapidly, allowing the plateau in the OS curve (and apparent difference in shape to CheckMate 057) to become apparent earlier. DOR was similar across studies, and treating patients with IO earlier in the treatment course, as well as the slightly higher ORR rate in CheckMate 057, means that OS at 3 and 4 years in the 057 cohort could be expected to be equal to, or above, that of CheckMate 003, in spite of the apparent difference in shape to date. On this basis, BMS thus believes the extrapolation of OS by the ERG to be clinically implausible.

- A comparison of CheckMate 003 with the Kaplan-Meier curve of OS in the ipilimumab registrational trial in advanced melanoma, as well as the pooled analysis, may serve as a second confirmatory model for what is seen in the CheckMate 057, since the patterns are highly similar. Notably, as seen with ipilimumab, a constant hazard appeared to exist in the first two years; however, this was followed by clear demonstration of decreasing hazards, shifting the shape of the OS curve, with a plateau appearing between 2-3 years and extending onward long-term.

We believe the data show that these immuno-oncologic agents can produce a trend towards long-term survival in a proportion of patients, which is unprecedented in NSCLC.

Table 2. Baseline Characteristics for Patients in CheckMate 003

Baseline characteristic	CheckMate 003 (N = 129)	CheckMate 057 (N = 292)
Median age, years (range)	65 (38 - 85)	61 (37-84)
Gender, n (%) Male	79 (61.2)	151 (52)
Tumour cell histology, n(%)		
Squamous	54 (41.9)	
Non-squamous	74 (57.4)	292 (100)
Unknown	1 (0.8)	
ECOG PS, n (%)*		
0 or 1	127 (98.4)	0: 84 (29) / 1: 208 (71)
2*	2 (1.6)	-
Number of prior systemic regimens, %		
1-2	59 (45.7)	1: 256 (88) / 2: 35 (12)
≥ 3	70 (54.3)	1 (< 1)
Nature of prior therapy		
Platinum-based	128 (99.2)	292 (100)

Baseline characteristic	CheckMate 003 (N = 129)	CheckMate 057 (N = 292)
chemotherapy		
Tyrosine kinase inhibitor	36 (27.9)	EGFR-TKI: 29 (9.9)
Surgery†	85 (65.9)	-
Radiotherapy†	75 (58.1)	-
Hormonal, immunologic, or biologic therapy	16 (12.4)	-
Other	9 (7.0)	-

Source: Borghaei et al. (2015); Gettinger et al. (2015)

Abbreviations: CR = Complete Response; ECOG = European Cooperative Oncology Group; EGFR = epidermal growth factor receptor; PS = Performance Status; SD = Stable Disease

*One patient in the CheckMate 003 study was enrolled before protocol amendment 4, which changed eligibility requirements from ECOG performance status of 0-2 to 0-1. A second patient was enrolled without evaluation of ECOG performance status at screening and had ECOG performance status of 2 at time of first nivolumab treatment. †Surgery and radiotherapy were not considered to be systemic therapies. ‡EGFR or KRAS mutational testing was not required for entry into this study; 41 (67%) of 61 patients with unknown EGFR tumour status and 43 (60%) of 72 patients with unknown KRAS tumour status had squamous cell histology; these patients likely were not tested for EGFR or KRAS mutations, because squamous non-small cell lung cancer rarely harbours EGFR or KRAS mutations.

Further, the OS curve for nivolumab seen in CheckMate 057 sits above that seen in CheckMate 003, which demonstrates improved survival; however, it follows the same trend. Therefore the CheckMate 003 study supports the concept of long-term survival in immuno-oncologics, and specifically, nivolumab in NSCLC. As such, this casts doubt on the ERG assumption that no long-term benefit exists with nivolumab. We therefore believe that the extrapolation provided below is appropriate, and can be considered a midway point between the ERG and BMS original extrapolations. The incremental cost-effectiveness ratios (ICERs) relating to this extrapolation are provided below.

Conclusion

Although long-term survival is not seen with chemotherapy, evidence exists from trials of immuno-oncology treatments demonstrating that their use can result in long-term survival.

Notably, although comparative studies of nivolumab in non-squamous NSCLC are not yet mature, the data are following the same trend as seen in other indications, as well as other immuno-oncology therapies. As such, these data do not support the ERG assumption of constant hazard (which was based on chemotherapeutic agents) and are supportive of long-term benefit, as anticipated by BMS. Therefore the current ERG approach to estimating survival is not a reasonable interpretation of the evidence and alternative approaches should be considered, as outlined below in the section entitled "Presentation of BMS new Base-Case Cost-effectiveness Analyses".

4.7 LONG-TERM OVERALL SURVIVAL EXTRAPOLATION: VALIDATION USING THE CHECKMATE 57 24-MONTH DATA

As described above, data from the 24-month data cut from CheckMate 057 have just become available (Borghaei et al., 2016). Within the time available we have used these data to validate the BMS and ERG survival extrapolations (which used the 12-month and 18-month data cut respectively)(NICE, 2016b). It is clear from Table 3 that the estimate for OS at 2 years using the 24-month data cutoff is in line with the previous estimates. The survival curves proposed by BMS and the ERG have not differentiated by this point (see Figure 6), and therefore the 24-month data does not support one approach over another. It is only from approximately 3 years follow-up that the BMS and ERG OS extrapolations begin to diverge, and therefore if relying on the CheckMate 057 data for validation of approach, at least another year of follow-up is required. The docetaxel curves are very similar using the two extrapolation curves and were not therefore explored.

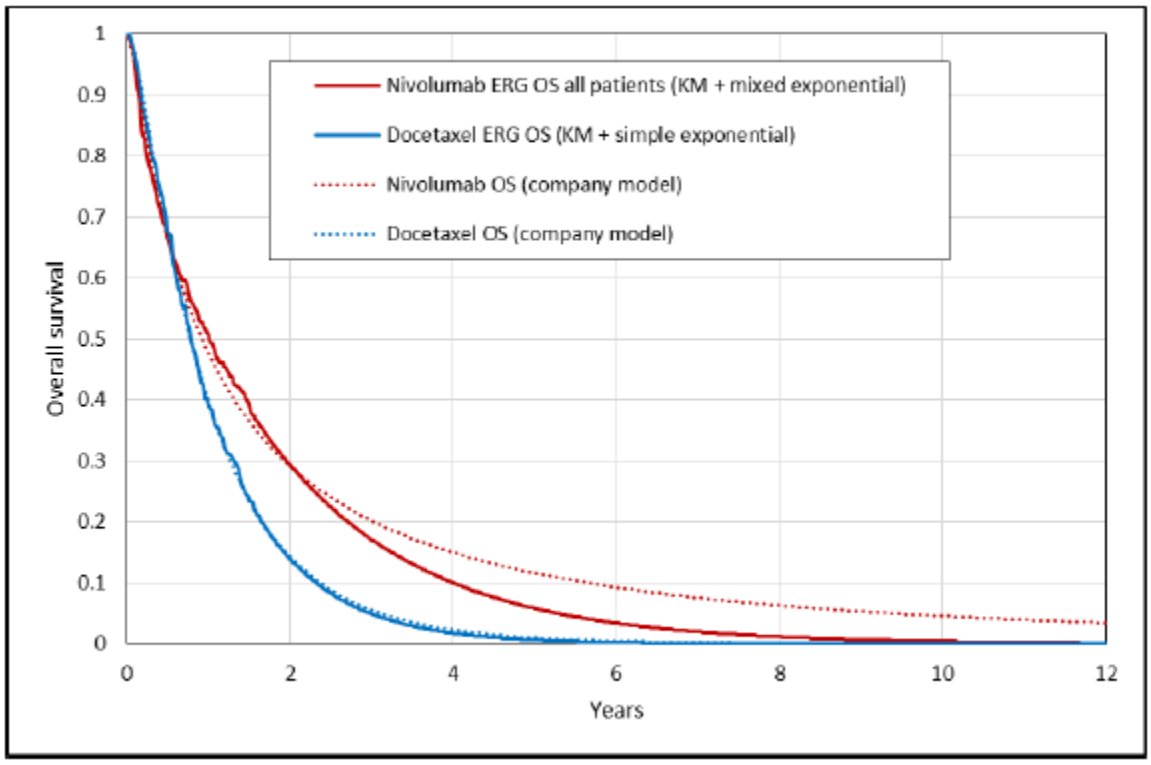
The estimate for rate of PFS at the 2-year data point is slightly higher using the 24-month cutoff than at previous cutoffs. Thus the data are reinforcing that long-term PFS is possible with nivolumab. The TTD data are also in line with previous estimates. It is anticipated that those patients who are still responding at 2 years will also have strong post-progression survival.

Table 3. Validation of Survival Analyses Using the 24-month Cutoff From CheckMate 057

Source	2-year point estimates for nivolumab			Mean estimates over model time horizon (20 years) for nivolumab (months)		
	TTD	PFS	OS	TTD	PFS	OS
BMS base-case UK model (12m - 057 data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMS UK model (18m - 057 data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG model (18m - 057 data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Checkmate 057 2-year data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Bristol-Myers Squibb, 2016c); Bristol-Myers Squibb (2016e).

Figure 6. Nivolumab and Docetaxel Overall Survival: ERG and Company Model (From ERG Report Figure 19)



Source: NICE (2016b).

4.8. COMPARISON WITH NINTEDANIB

The ERG's comparison of nivolumab and nintedanib + docetaxel, used in the economic model was based on the assumption that the docetaxel arms in the two studies (LUME-Lung 1 and CheckMate 057) were reasonably similar, meaning that an unadjusted indirect comparison could be made (NICE, 2016b). In terms of the statistical approach, conducting an unadjusted comparison does not respect the randomisation of the trials, so even if a small (non-statistically significant) difference is observed between the docetaxel arms, which may be important and could affect the extrapolation. Therefore, current guidance does not recommend that unadjusted comparisons are used (Jansen et al., 2011).

It is also important to note that there are some key differences between the two studies that place the ERG's assumption into doubt and mean that cross-trial comparisons should be treated with caution (Reck et al., 2014). In particular, there are differences in the proportion of patients each study who were male or current/former smokers (Table 4). In addition, there is an absence of important prognostic information relating to the adenocarcinoma-only subgroup of LUME-Lung 1, namely (Reck et al., 2014):

- Stage of disease

- CNS metastases (not available for the adenocarcinoma subpopulation)
- Best response to most recent prior systemic treatment
- Time from completion of most recent systemic treatment.

Table 4. Baseline Characteristics in LUME-Lung 1 and Checkmate 057

	CheckMate 057		LUME-Lung 1 (adenocarcinoma)	
	Docetaxel	**Nivolumab**	**Docetaxel**	**Nintedanib + docetaxel**
PS 1 (%)	67	71	71	71
EGFR mutant (% negative/unknown)	80	80	All unknown	All unknown
Median age (yrs)	64	61	60	60
Male (%)	58	52	73	73
Current/former smoker (%)	78	79	76	75

*Please note this includes all patients with advanced NSCLC (not limited to those with adenocarcinoma)

Sources: Borghaei et al. (2015); Reck et al. (2014)

These known differences in baseline characteristics, along with the uncertainty in other characteristics means that we cannot assume the populations in the two studies are the same, and therefore the unadjusted indirect comparison of nivolumab and nintedanib + docetaxel should be treated with caution.

Finally, in line with the explanation in the section 'Long-term overall survival benefit of nivolumab' above, it is anticipated that nivolumab will exhibit greater long-term overall survival than traditional chemotherapy. Therefore, as for the comparison with docetaxel, it is inappropriate to fit an exponential to both curves (assuming a constant hazard of death), when long-term survival is likely for nivolumab, which is seen in terms of decreasing hazard of death.

4.9 PROGRESSION-FREE SURVIVAL VERSUS TIME TO TREATMENT DISCONTINUATION

As noted in the ACD, in the company submission model, we used time to treatment discontinuation (TTD) rather than progression-free survival (PFS), to model the PFS health state (NICE, 2016a). This was due to the assumption that patients who are treated with nivolumab post-progression continue to receive a clinical benefit. In their review of this model, the ERG suggest that TTD is used to model costs and PFS to model benefits (NICE, 2016b). However, this ignores the benefit that those patients treated post-progression continue to receive from nivolumab.

In CheckMate 057, patients in the nivolumab arm could receive nivolumab after progression if they met certain criteria including investigator-assessed clinical benefit and no rapid disease progression; tolerance of study drug and stable performance status (Bristol-Myers Squibb, 2013). This allowance was made in the study protocol due to accumulating evidence that patients may continue to gain benefit because standard response definitions, such as RECIST or WHO, do not provide a complete assessment of immuno-oncologic agents, and might incorrectly suggest initial evidence of progressed disease (PD) (Wolchok et al., 2009).

In order for a patient to receive treatment after progression in CheckMate 057, the physician had to feel that a patient continued to achieve clinical benefit from receiving treatment and ensure that there was no deterioration in performance status; treatment was stopped upon any further progression (Bristol-Myers Squibb, 2013). This means that those patients receiving nivolumab post-progression were more akin to the "PFS" health state, than the "PD" one in terms of both costs and outcomes, and were certainly not the equivalent of patients with progressed disease in the van den Hout study, who by definition had PS2 (van den Hout et al., 2006), that the ERG have recommended be used to quantify HRQoL in patients with progressed disease (see 4.11 below)(NICE, 2016b).

By using TTD to model both costs and benefits, this difference in the health state of patients treated post-progression is captured in terms of both costs and benefits. Whereas using the ERG approach means that these patients are still accruing all the costs of treatment but are assumed to receive no benefit. We therefore consider that TTD is the most appropriate outcome for modelling the PFS health state.

4.11 ASSESSMENT OF UTILITY

Progressed Disease

The ERG approach to estimating utility for the PD heath state uses the van den Hout et al. (2006) study, which is representative of the EQ-5D of patients with stage III or IV NSCLC who were treated with palliative radiotherapy for symptomatic relief. In order for this to be appropriate, the health related quality of life of PD patients in CheckMate 057 would have to be equivalent to palliative care patients in the Van den Hout et al. publication.

However, the majority of patients in van den Hout et al. (2006) had ECOG performance status (PS) of 2 or more, and patients receiving systemic chemotherapy were excluded (van den Hout et al., 2006). Conversely, patients enrolled in the CheckMate 057 study all had a PS0-1 (Borghaei et al., 2015). Further, over half of patients (42% nivolumab; 50% docetaxel) went on to receive a 3rd line systemic treatment following progression (Borghaei et al., 2015); these progressed patients would have had a better prognosis in order to receive such 3rd line systemic treatment, and are thus not reflective of symptomatic patients receiving radiotherapy. Similarly, those patients who continued to receive nivolumab post-

progression continued to gain clinical benefits from treatment, but would be considered to be in the PD health state using the ERG approach. Clearly, the health related quality of life of these patients would not be that of a patient with PS2 NSCLC receiving palliative radiotherapy and end-of-life care.

As such, the populations in the Van den Hout et al. (2006) study and the CheckMate 057 study cannot be considered equivalent and the use of the van den Hout et al. (2006) estimate of utility for patients with PD is a large under-estimation for the patient population under consideration.

Further, NICE have previously accepted the following utilities for PD in recent appraisals:

- Nivolumab in squamous NSCLC (TA811): [redacted] (NICE, 2015a)
- Nintedanib (TA347): 0.64 (NICE, 2015b)
- Erlotinib and gefitinib (TA374): 0.47 (NICE, 2015c)

We anticipate that patients in the nivolumab in squamous NSCLC, and nintedanib appraisals are similar to those in the non-squamous NSCLC population, and as such, argue that the utilities applied by the ERG to this population are inappropriate.

We thus consider the utilities used by BMS to be more appropriate, as well as in line with the reference case. We accept the appraisal committee's suggestion that a disutility for end-of-life should be applied (NICE, 2016a). However, there are few data around end-of-life utilities in NSCLC, and definitions vary between these. We identified one study by Viganò et al. (1999) where patients spent approximately 4 weeks in a hospice setting (Vigano et al., 1999). We have therefore applied the PD end-of-life health utility from van den Hout et al. (2006) for twice this duration (8 weeks) as a conservative estimate within revised utility calculations presented in our revised base-case presented in the section "Presentation of BMS new Base-Case Cost-effectiveness Analyses" below.

PRESENTATION OF BMS NEW BASE-CASE COST-EFFECTIVENESS ANALYSES

BMS has considered the recommendations of the ERG (NICE, 2016b), the findings of the AC (NICE, 2016a) and the newly available 24-month data cut from CheckMate 057 (Borghaei et al., 2016) and provide a new base-case cost-effectiveness analysis below (Bristol-Myers Squibb, 2016a).

Updates to the Previous BMS Base-Case Model

The BMS model has been updated based on the ERG's review to incorporate appropriate changes, or identify alternative scenarios that address the ERG's concern (Bristol-Myers Squibb, 2016c). The errors that the ERG identified in terms of the costs of nivolumab and

applying costs at the start of each cycle have been corrected. In addition, the following change have been made in line with our responses above:

- New long-term survival models based on the 24-month data from CheckMate 057 (see below)
- Revised utility value for the PD health state of 0.650. This is a weighted utility, incorporating a disutility to account for end-of-life (0.476), based on van den Hout et al. (2006), into the estimate based on CheckMate 057 data (0.688).

In line with our reasoning above, we have utilised TTD to model the PFS health state and our approach to compare nivolumab and nintedanib (Bristol-Myers Squibb, 2016a).

Alternative Extrapolations Based on Hazard Profile

Long-term survival data for new therapies such as immuno-oncologics are only now becoming available. The most appropriate OS extrapolation needs to reflect this emerging evidence and the evidence available to date shows that the hazard for mortality decreases over time.

While we strongly disagree with the ERG's specific OS extrapolation (NICE, 2016b), based on the incorrect assumption of a constant hazard past a certain point, we do recognise that hazard profiles provide useful insight into how long-term survival may be modelled. We have reassessed plausible OS extrapolations based on the 24-month data from CheckMate 057 and expected hazard profile over time, and suggest that either the log-normal or log-logistic extrapolations provide a reasonable alternative, based on the ERG's preferred approach but appropriately reflecting the data available for immuno-oncologic agents.

In line with BMS' initial submission (NICE, 2016b), a range of survival analyses for both OS and TTD were undertaken and assessed for fit based on AIC/BIC, in line with DSU recommendations (Latimer, 2013). In addition, those factors highlighted by the ERG (patients not surviving longer than the general population and OS and PFS/TTD not crossing)(NICE, 2016b) were assessed when identifying the most valid curves.

For both OS and TTD, log-normal was the best fitting curve for both nivolumab and docetaxel in terms of AIC and BIC and all of the other clinical validity checks and we present this as our base-case (Bristol-Myers Squibb, 2016c). As we recognise that the appraisal committee felt our extrapolation was too optimistic and we have shown the ERG approach to be too conservative (NICE, 2016a), we identified other extrapolations that meet the clinical validity criteria while acknowledging this concern. Of these, the most plausible scenario was the use of generalised gamma for OS and log-normal for TTD. Although the ERG criticised the use of a generalised gamma survival model when based on the 12-month data cut (NICE, 2016b), this new extrapolation, based on the 24-month data cut does not

have the same validity issues and provides a valid alternative scenario, in between the BMS base-case and ERG approach.

The OS extrapolations for nivolumab are presented in Figure 7, for the 24-month data cut; this includes the best fitting curves (log-normal and generalised gamma) as well as the exponential (Bristol-Myers Squibb, 2016c). It also includes the ERG curve using the 18 month data and the generalised gamma curve from BMS' original submission, which was based on the 12-month data (NICE, 2016b).

Figure 7. Overall Survival Extrapolations for Nivolumab

Source: Bristol-Myers Squibb (2016c). Note: this figure is academic in confidence

Summary Results at List Price

Based on the model revisions outlined, results are presented in Table 5 for both the base-case (log-normal for both OS and TTD) and the alternative scenario (generalised gamma for OS, log-normal for TTD (Bristol-Myers Squibb, 2016c). These results assume the costs of nivolumab at list price.

Table 5. Results of the Revised Cost-effectiveness Model Using 24-month Data, Nivolumab at List Price

Treatment	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost per QALY (£)
Base-case (log-normal for both OS and TTD)							
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	106,653
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	177,698
Alternative scenario (generalised gamma for OS, log-normal for TTD)							
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	114,235
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	163,798

Source: Bristol-Myers Squibb (2016c)

Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was conducted using a second-order Monte Carlo simulation run for 1,000 iterations, using the parameters outlined in our original submission. Results of the PSA for the base-case are shown below for both the BMS base case and alternative scenario (Bristol-Myers Squibb, 2016c).

BMS base case model

Table 6. Results of Probabilistic Sensitivity Analysis: BMS base case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Probablistic values					
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	110,658
Docetaxel	[redacted]	[redacted]	[redacted]		
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	182,189
Deterministic values					
Docetaxel			[redacted]	[redacted]	106,653
Nintedanib plus docetaxel			[redacted]	[redacted]	177,698

Figure 8. Scatter Plot for Cost-effectiveness of Nivolumab Versus Docetaxel (1,000 iterations): BMS Base Case

Note: this figure is academic in confidence

Figure 9. Scatter Plot for Cost-effectiveness of Nivolumab Versus Nintedanib + Docetaxel (1,000 iterations): BMS Base Case

Note: this figure is academic in confidence

Figure 10. Cost-effectiveness Acceptability Curve of Nivolumab Versus Docetaxel and Nintedanib in Combination With Docetaxel: BMS Base Case

Note: this figure is academic in confidence

A one-way sensitivity analysis was undertaken by varying cost, utility and OS base-case parameter values by their CIs (where available) or ±20% in line with the approach in our original submission, results are presented below (Bristol-Myers Squibb, 2016c).

Table 7. Results of Deterministic Sensitivity Analysis Versus Docetaxel: BMS Base Case

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Baseline		[redacted]	[redacted]	106,653
Discount rate - costs	Lower	[redacted]	[redacted]	113,069
	Higher	[redacted]	[redacted]	103,034
Discount rate - outcomes	Lower	[redacted]	[redacted]	89,488
	Higher	[redacted]	[redacted]	118,738

Average body weight	Lower	[redacted]	[redacted]	88,917
	Higher	[redacted]	[redacted]	124,691
Body surface area	Lower	[redacted]	[redacted]	106,750
	Higher	[redacted]	[redacted]	106,471
Costs		[redacted]	[redacted]	
Cost - PF state	Lower	[redacted]	[redacted]	106,046
	Higher	[redacted]	[redacted]	107,259
Cost - PD state	Lower	[redacted]	[redacted]	105,593
	Higher	[redacted]	[redacted]	107,713
Cost - terminal	Lower	[redacted]	[redacted]	106,693
	Higher	[redacted]	[redacted]	106,612
Admin cost - nivolumab	Lower	[redacted]	[redacted]	105,344
	Higher	[redacted]	[redacted]	107,961
Admin cost - Comparator	Lower	[redacted]	[redacted]	107,061
	Higher	[redacted]	[redacted]	106,244
Monitoring cost - nivolumab	Lower	[redacted]	[redacted]	106,074
	Higher	[redacted]	[redacted]	107,231
Monitoring cost - comparator	Lower	[redacted]	[redacted]	106,908
	Higher	[redacted]	[redacted]	106,398
Outcomes		[redacted]	[redacted]	
Utility weight, PFS, no response	Lower	[redacted]	[redacted]	107,452
	Higher	[redacted]	[redacted]	105,943
Utility weight, PD	Lower	[redacted]	[redacted]	106,201
	Higher	[redacted]	[redacted]	103,621

Figure 11. Tornado Diagram for Nivolumab Versus Docetaxel: BMS Base Case

Note: this figure is academic in confidence

Table 8. Results of Deterministic Sensitivity Analysis Versus Nintedanib + Docetaxel: BMS Base Case

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Baseline		[redacted]	[redacted]	177,698
Discount rate - costs	Lower	[redacted]	[redacted]	188,397
	Higher	[redacted]	[redacted]	171,589
Discount rate - outcomes	Lower	[redacted]	[redacted]	147,663
	Higher	[redacted]	[redacted]	198,684
Average body weight	Lower	[redacted]	[redacted]	137,678
	Higher	[redacted]	[redacted]	218,401
Body surface area	Lower	[redacted]	[redacted]	177,920
	Higher	[redacted]	[redacted]	177,289
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	176,344
	Higher	[redacted]	[redacted]	179,051
Cost - PD state	Lower	[redacted]	[redacted]	178,864

	Higher	[redacted]	[redacted]	176,532
Cost - terminal	Lower	[redacted]	[redacted]	177,736
	Higher	[redacted]	[redacted]	177,660
Admin cost - nivolumab	Lower	[redacted]	[redacted]	174,745
	Higher	[redacted]	[redacted]	180,651
Admin cost - Comparator	Lower	[redacted]	[redacted]	178,730
	Higher	[redacted]	[redacted]	176,666
Monitoring cost - nivolumab	Lower	[redacted]	[redacted]	176,392
	Higher	[redacted]	[redacted]	179,003
Monitoring cost - comparator	Lower	[redacted]	[redacted]	178,348
	Higher	[redacted]	[redacted]	177,048
Outcomes				
Utility weight, PFS, no response	Lower	[redacted]	[redacted]	180,697
	Higher	[redacted]	[redacted]	175,082
Utility weight, PD	Lower	[redacted]	[redacted]	178,533
	Higher	[redacted]	[redacted]	183,604
Survival Outcomes				
HR on PFS - Comparator	Lower	[redacted]	[redacted]	172,535
	Higher	[redacted]	[redacted]	180,915
HR on OS - Comparator	Lower	[redacted]	[redacted]	-878,944
	Higher	[redacted]	[redacted]	99,730

Figure 12. Tornado Diagram for Nivolumab Versus Nintedanib + Docetaxel: BMS Base Case

Note: this figure is academic in confidence

BMS alternative scenario

Table 9. Results of Probabilistic Sensitivity Analysis: BMS Alternative Scenario

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Probablistic values					
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	112,538
Docetaxel	[redacted]	[redacted]			
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	152,635
Deterministic values					
Docetaxel			[redacted]	[redacted]	114,235
Nintedanib plus docetaxel			[redacted]	[redacted]	163,798

Figure 13. Scatter Plot for Cost-effectiveness of Nivolumab Versus Docetaxel (1,000 iterations): BMS Alternative Scenario

[redacted]

Note: this figure is academic in confidence

Figure 14. Scatter Plot for Cost-effectiveness of Nivolumab Versus Nintedanib + Docetaxel (1,000 iterations): BMS Alternative Scenario

Note: this figure is academic in confidence

Figure 15. Cost-effectiveness Acceptability Curve of Nivolumab Versus Docetaxel and Nintedanib in Combination With Docetaxel: BMS Alternative Scenario

Note: this figure is academic in confidence

A one-way sensitivity analysis was undertaken by varying cost, utility and OS base-case parameter values by their CIs (where available) or ±20% in line with the approach in our original submission, results are presented below (Bristol-Myers Squibb, 2016c).

Table 10. Results of Deterministic Sensitivity Analysis Versus Docetaxel: BMS Alternative Scenario

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Baseline		[redacted]	[redacted]	114,235
Discount rate - costs	Lower	[redacted]	[redacted]	120,450
	Higher	[redacted]	[redacted]	110,658
Discount rate - outcomes	Lower	[redacted]	[redacted]	98,561
	Higher	[redacted]	[redacted]	125,184
Average body weight	Lower	[redacted]	[redacted]	95,037
	Higher	[redacted]	[redacted]	133,762

Body surface area	Lower	[redacted]	[redacted]	114,341
	Higher	[redacted]	[redacted]	114,039
Costs		[redacted]	[redacted]	
Cost - PF state	Lower	[redacted]	[redacted]	113,579
	Higher	[redacted]	[redacted]	114,892
Cost - PD state	Lower	[redacted]	[redacted]	113,338
	Higher	[redacted]	[redacted]	115,133
Cost - terminal	Lower	[redacted]	[redacted]	114,271
	Higher	[redacted]	[redacted]	114,199
Admin cost - nivolumab	Lower	[redacted]	[redacted]	112,819
	Higher	[redacted]	[redacted]	115,652
Admin cost - Comparator	Lower	[redacted]	[redacted]	114,678
	Higher	[redacted]	[redacted]	113,793
Monitoring cost - nivolumab	Lower	[redacted]	[redacted]	113,609
	Higher	[redacted]	[redacted]	114,862
Monitoring cost - comparator	Lower	[redacted]	[redacted]	114,511
	Higher	[redacted]	[redacted]	113,959
Outcomes				
Utility weight, PFS, no response	Lower	[redacted]	[redacted]	115,163
	Higher	[redacted]	[redacted]	113,413
Utility weight, PD	Lower	[redacted]	[redacted]	113,825
	Higher	[redacted]	[redacted]	111,475

Figure 16. Tornado Diagram for Nivolumab Versus Docetaxel: BMS Alternative Scenario

Note: this figure is academic in confidence

Table 11. Results of Deterministic Sensitivity Analysis Versus Nintedanib + Docetaxel: BMS Alternative Scenario

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Baseline		[redacted]	[redacted]	163,798
Discount rate - costs	Lower	[redacted]	[redacted]	173,656
	Higher	[redacted]	[redacted]	158,133
Discount rate - outcomes	Lower	[redacted]	[redacted]	137,787
	Higher	[redacted]	[redacted]	182,147
Average body weight	Lower	[redacted]	[redacted]	127,199
	Higher	[redacted]	[redacted]	201,021
Body surface area	Lower	[redacted]	[redacted]	164,001
	Higher	[redacted]	[redacted]	163,423
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	162,560
	Higher	[redacted]	[redacted]	165,035
Cost - PD state	Lower	[redacted]	[redacted]	164,604
	Higher	[redacted]	[redacted]	162,991
Cost - terminal	Lower	[redacted]	[redacted]	163,832

	Higher	[redacted]	[redacted]	163,763
Admin cost - nivolumab	Lower	[redacted]	[redacted]	161,097
	Higher	[redacted]	[redacted]	166,498
Admin cost - Comparator	Lower	[redacted]	[redacted]	164,742
	Higher	[redacted]	[redacted]	162,854
Monitoring cost - nivolumab	Lower	[redacted]	[redacted]	162,604
	Higher	[redacted]	[redacted]	164,992
Monitoring cost - comparator	Lower	[redacted]	[redacted]	164,392
	Higher	[redacted]	[redacted]	163,203
Outcomes				
Utility weight, PFS, no response	Lower	[redacted]	[redacted]	166,323
	Higher	[redacted]	[redacted]	161,590
Utility weight, PD	Lower	[redacted]	[redacted]	164,330
	Higher	[redacted]	[redacted]	167,527
Survival Outcomes				
HR on PFS - Comparator	Lower	[redacted]	[redacted]	158,617
	Higher	[redacted]	[redacted]	167,042
HR on OS - Comparator	Lower	[redacted]	[redacted]	934,566
	Higher	[redacted]	[redacted]	105,123

Figure 17. Tornado Diagram for Nivolumab Versus Nintedanib + Docetaxel: BMS Alternative Scenario

Note: this figure is academic in confidence

CONCLUDING REMARKS

Nivolumab is an innovative treatment option that offers a survival and HRQoL benefit as well as reduced toxicity to patients with non-squamous NSCLC who have received prior therapy. This represents a remarkable further advancement in the NSCLC treatment pathway and has been recognised as a noteworthy step-change in the management of this life-threatening condition. In consideration of the proposed PAS (results provided in Appendix), Nivolumab is a cost effective treatment option for patients with non-squamous NSCLC who have received prior therapy.

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Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Nivolumab for previously treated, locally advanced or metastatic non squamous non small cell lung cancer. [ID 900]

This response is submitted by Roy Castle Lung Cancer Foundation.

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

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

    - Nivolumab is a clinically effective treatment option for previously treated non squamous non small cell lung cancer, compared with Docetaxel, Docetaxel/Nintedanib and Best Supportive Care (section 4.3, 4.4)

    - Nivolumab is an innovative therapy (section 4.17)

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

- We note that the Appraisal Committee has reached this negative decision, based on cost issues - Nivolumab, having not been deemed a cost effective use of NHS resources. (section 4.19). We note the Appraisal Committee's conclusion that the "most plausible incremental cost-effectiveness ration for Nivolumab, compared with Docetaxel is £91,100 per quality adjusted life year gained". And the "most plausible ICER for Nivolumab, compared with Docetaxel and Nintedanib is £93,400 per quality adjusted life year gained" (section 4.12 and 4.13)

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

Roy Castle Lung Cancer Foundation
June 2016

Response ACD- Consultees & Commentators: Lung cancer(non-small cell non-squamous, metastatic, after treatment)Nivolumab (900)

Response from NLCFN

NLCFN emphasised that there is a high unmet need for this patient group since current treatment options are limited and many patients are unable to tolerate the side effects of current treatments. Relapsed non-squamous NSCLC has debilitating and distressing symptoms, therefore improving quality of life and even a small extension to life would and should be considered as a significant benefit by both patients and their families.

Received by email:

Dear Stephanie

The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation.

We note that NICE have taken due consideration that nivolumab is an innovative treatment which gives a survival advantage and, therefore, feel there will be little ground for appeal.

We understand the importance of cost effectiveness and would support any moves by either the drug companies involved or NICE to ensure all avenues are explored to ensure innovative treatments are available for patients.

I would be grateful if you could confirm receipt.

Best wishes

[redacted] | [redacted]
Membership Support and Global Engagement Department| Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE

To,
Meindert Boysen
Programme Director,
Centre for Health Technology Evaluation
Level 1A, City Tower, Piccadilly Plaza
Manchester, M1 4BT

03 June 2016

Dear Meindert,

Please find below our comments on the ACD on ID900: Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer.

Has all of the relevant evidence been taken into account?

1. Nivolumab European Public Assessment Report (EPAR), EMA/246304/2016, dated 25 February 2016, and updated summary of product characteristics (SmPC) contain new, partly previously unpublished results, and the following conclusions:
    a. Early death rates (i.e. within 3 months): The EPAR notes (pages 36-37, Figure 11) "The docetaxel group shows a similar death rate across the different baseline groups according to baseline PD-L1 expression. The additional post hoc analyses revealed that for nivolumab patients with a baseline PD-L1 expression <10%, the early death rate was around 25%; this death rate is higher than for docetaxel. In contrast, patients with a PD-L1 expression ≥ 50% nivolumab show a low overall early death rate (6.8%, which is lower than observed with docetaxel 24%)." It concludes that "Therefore, it is cannot be ruled out that the baseline PD-L1 expression percentage may affect the early death rate."
    b. The EPAR also notes that "Regarding OS benefit and other key efficacy results according to baseline PD-L1 status, it is noted that results in PD-L1 negative/non-quantifiable patients are similar to those seen in the docetaxel patients, with practically no differences between this subset of patients and those in the docetaxel group, with numerically more deaths in nivolumab patients than docetaxel during the first 6 months of treatment."

2. The Checkmate-057 publication (Borghaei, 2015) Supplementary Appendix reports:
    a. Significant interaction P-values of PD-L1 expression for both PFS and OS (figure S7) indicating a strong effect modification by PD-L1 levels.
    b. Kaplan Meier curves for PFS (figure S8A) and OS (figure S8B) at the 1%, 5% and 10% PD-L1 Expression Levels, showing a the influence of the PD-L1 cut-off used on the crossing of the curves. This could lead to potential alternative solutions to the currisng OS curves issue discussed in the comment #3 below.

3. Alternative causality and solutions for the crossing OS curves
    a. The manufacturer's submission mentions the issue of the "crossing of the OS curves" (page 150-151 of the manufacturer's submission, Figure 28), however only suggests "pseudo-progression" as a possible cause for this. We support the ERG in its statement "The ERG is not convinced that the data presented support this claim" and that "a number of theories exist for this delay, and the exact underlying

mechanism is unclear" (pages 11 and 36, respectively, of the ERG submission).

b. The additional information in the EPAR and SmPC (#1 above) might form a plausible alternative explanation where early deaths in patients with low PD-L1 expression might help explain the crossing curves. It could therefore be important to consider the OS curves for different PD-L1 cut-off levels in trying to solve the issue of the crossing curves.

4. While we understand that considering the post-hoc nature of these analyses and the limited size of some of the subgroups and that these results need to be taken with caution, these additional points could be considered in this assessment, especially as the highest benefits of nivolumab appear to be observed at PD-L1 cut-off of 50%.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

5. ACD Section 4.3: In view of our comments #1-4 above (new data in the EPAR, SmPC, as well as existing data in the Supplementary Appendix of the Checkmate-057 publication (Borghaei, 2015), the conclusions about clinical benefits in survival may have to be reconsidered based on the PD-L1 expression levels; as well as the data on the early mortality.

6. ACD section 4.4: While the committee accepted that the indirect treatment comparison "was not a reliable estimate of comparative effectiveness", it goes on to conclude a gain in quality of life with nivolumab based on avoidance of toxicities associated with docetaxel based on clinical and patient expert comments. However, based on the early mortality data and the PD-L1 cut-off (our comments #1-4 above), the subgroups of patients with ≤50% PD-L1 expression could be considered to have better overall survival with docetaxel than nivolumab and therefore accrue higher QALYs with docetaxel than with nivolumab.

7. ACD section 4.5: We support the committee's conclusion that "it could be plausible that nivolumab might have a different level of clinical effectiveness according to PD-L1 expression." The current clinical or cost-effectiveness estimates do not however take this into account, even though this in itself might help to explain and solve the crossing OS curves (by accounting for the increased early mortality by PD-L1 expression levels, and accounting for differential efficacy of nivolumab vs docetaxel based again on PD-L1 expression levels).

8. ACD sections 4.6-4.9: In modelling OS for comparing nivolumab to both docetaxel and nintedanib + docetaxel, "the proportional hazards assumption was not met", primarily due to the crossing curves. The solution adopted by the ERG was to use 18-month data and an exponential extrapolation. However, given our comments # 1-4 above, we'd suggest that PD-L1 expression level was a key effect modifier, and therefore should be used to model survival outcomes.

9. ACD Section 4.13 and 'Summary of appraisal committee's key conclusions', box 'key conclusions': The fourth (of five) bullet points currently states "The most plausible ICER for nivolumab compared with nintedanib plus docetaxel was £93,400 per QALY gained". While the text in section 4.13 clarifies that this figure does not include the existing PAS for nintedanib (and that including this would make the most likely ICER to be much higher), the summary table omits this clarification. For increased clarity, we would propose the statement in the summary table to also reflect this fact that the ICER quoted does not account for the PAS for nintedanib and is therefore an underestimation.

Are the recommendations sound and a suitable basis for guidance to the NHS?

10. While we support the recommendations in the ACD, we would propose that a stronger case exits with recent and existing data on early mortality and effect of PD-L1 expression on treatment effect to make any reconsideration of the recommendation contingent on the PD-L1 cut-off levels.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

11. Not to our knowledge at this point.

Thanks for the opportunity to comment on this.

Best wishes,

[redacted], Boehringer Ingelheim Ltd
Ellesfield Avenue, Bracknell, Berkshire. RG12 8YS
Tel: [redacted] | Mobile: [redacted]

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

Name	[redacted]
Role	NHS Professional
Other role	Consultant
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD: I am very convinced by the data about Nivolumab for lung. We are already using it for Melanoma and for lung via EAMS. I would request NICE to reconsider their decision to make this available for patients with lung cancer . This will be a valuable treatment for the patient	
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	Lung Cancer Nurse Specialist
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD: Just to express concern that nivolumab is not available for pts with lung cancer. We have had one pt who decided to fund privately, although funds were tight.We have a lot of pts asking about the drug and I think pts will be v distressed to hear that it is available for some tumour groups and not others	
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	Consultant Clinical Oncologist, [redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Nivolumab is an important new treatment for patients with non-squamous non-small cell lung cancer.

I've had a large lung cancer practice since taking up my consultant job 18 years ago. I've therefore practiced through the arrival and evolution of both chemotherapy and biological / targeted agents for NSCLC.

Whilst it is fantastic to have access to EGFR TKI and ALK inhibitors the reality of a lung cancer practice in a predominantly Caucasian northern city is that well below 10% of patients carry those mutations.

First line chemotherapy has now evolved significantly with choices of a number of effective modern agents with tolerable toxicity profiles.

However second line treatment options remain dismal. Docetaxol has a very modest response rate and a very high toxicity burden with overwhelming fatigue which hugely limits its use in day to day clinical practice.

Nivolumab on the other hand offers a novel and innovative approach and a vastly different toxicity profile. Whilst a small number of patients do have troublesome immune mediated side effects they are relatively few and in real life this is a very well tolerated drug.

The magnitude of the differences in OS at 12 and 18 months are not to be underestimated in a lung cancer practice.

This drug / this class of drugs represent a breakthrough in the treatment of non-small cell lung cancer and are sufficiently innovative to be awarded MHRA EAMS status.

Therefore it is difficult to understand why NICE have concluded that Nivolumab should not be recommended.

Nivolumab and other drugs in this class will change the practice of oncology and this country can not be late adaptors of this hugely significant advance in practice.

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	Consultant Clinical Oncologist
Organisation	
Location	England
Conflict	
Notes	

Comments on individual sections of the ACD:

I recommend the committee reconsider the evidence as this drug does present a paradigm shift in the treatment of NSCLC - there is clinical efficacy with reduced toxicity compared to other active agents.

Restricting to those with PD1 expression may be helpful in focusing treatment on those most likely to benefit; negotiating a cost reduction with the company may be possible given the increasing indications for nivolumab

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	Consultant Oncologist
Organisation	
Location	England
Conflict	No
Notes	Oncologist treating lung cancer and melanoma

Comments on individual sections of the ACD:
NICE has done a well balanced appraisal. No equality issues are noted. Cost effective analysis is largely acceptable.

But as there is a real unmet need in Nonsquamous lung cancer, this treatment could make a significant impact on many lives. The company should co operate with NICE to identify at least a small subgroup of patients (eg. pDL 1 expression, good performance status, 0,1; second or third line treatment etc.,)

Immunotherapy holds large promise . I sincerely hope that a cost effective treatment protocol will be a stepping stone in the right direction.

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	Consultant Medical Oncologist, [redacted]
Organisation	
Location	England
Conflict	Yes
Notes	I recruit patients to many clinical trials, some of which have been funded by BMS. This funding compensates the clinical research team & hospital for work done, and I receive no personal payment

Comments on individual sections of the ACD:
This technology offers the prospect of outstanding benefit to some patients with a disease hitherto associated with a quite dismal outlook. I believe it would be perverse for the NHS in England not to be able to offer this groundbreaking therapy

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	Clinical Oncology Consultant
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Having used Nivolumab through clinical trials and in the private sector, I have seen a number of patients have significantly improved length and quality of life as a result of this drug.

It has clinical data to show clear improval for these lung cancer patients. A large number of my patients regularly ask for when it will be available for them on the NHS, as it is their only hope.

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	Locum Consultant Oncologist
Organisation	
Location	England
Conflict	No
Notes	I care about people being free of suffering, loving their lives, and knowing that they matter and are appreciated. Thank you.

Comments on individual sections of the ACD:

The overall survival benefit associated with Nivolumab, for the whole group of patients studied in checkmate 057 of just under 3 months is a big bonus for a drug that really does seem less "toxic" than the standard alternative docetaxel, which in my experience, is a drug we are trying to find alternatives to, as gut feeling from experience is it really doesn't add a lot of benefit to the lives of patients on average, even if there is some evidence behind it. Although the Checkmate 057 trial was not powered for results by PD-L1 status, the subgroup analysis is compelling. This drug appears in a significant proportion of patients - looks like about 40% to me - to have a benefit of 9-10 months extension of overall survival. I do not know what the cost analysis is, but this looks like very good news to me, in a sad and difficult disease. I do hope that the drug is cost effective. I think Lung cancer patients have a higher than average rate of making the most of any extension of their lives!! Thank you for considering my comments.

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)	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

August 2015

1 Introduction

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

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

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

2 Instructions for manufacturers and sponsors

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

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

Please refer to the following documents when completing the template:

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

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

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

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

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

When making a patient access scheme submission, include:

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

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

3 Details of the patient access scheme

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

Generic Name: Nivolumab

Brand Name: Opdivo®

Disease area: Lung Cancer

Indication: Previously treated adults with locally advanced or metastatic non-squamous NSCLC (nsqNSCLC).

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

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

There are currently limited treatment options available for patients diagnosed with previously treated nsqNSCLC. Current therapy, docetaxel, has poor response rates and limited efficacy. Nintedanib in combination with docetaxel was also approved by NICE in patients with adenocarcinoma (approximately 90% of nsqNSCLC patients) in 2015, but use is currently low (Figure 3 in the CS).

Opdivo® provides an unprecedented survival benefit (27% reduction in death compared with standard of care) in patients in whom docetaxel is poorly tolerated and has poor efficacy, a step-change in comparison to therapeutic alternatives.

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

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

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

The proposed Opdivo® patient access scheme (PAS) will apply to all patients covered by NICE guidance for Opdivo® for previously treated adults with locally advanced or metastatic nsqNSCLC, covered in this submission [ID 900]. If the NICE committee recommends nivolumab for the two lung appraisals [ID 811 and 900] then this simple PAS will also apply across all the other licensed indications of nivolumab (melanoma monotherapy [TA 384], regimen [ID848], and RCC [ID 853]. NICE has already recommend nivolumab for melanoma monotherapy and regimen at list price so this represents an additional saving to the NHS.

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

- Why have the criteria been chosen?

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

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

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

Table 1. Population eligible for the scheme

Population	**Proportion of patients**	**Number of patients**	**Reference**
Total NSCLC	N/A	27,300	(Health and Social Care Information Centre 2014)
Patients with stage IIIb/IV NSCLC	N/A	19,138	(Health and Social Care Information Centre 2014)
Non-squamous NSCLC	64.35%	12,315	(Powell 2013)
Patients who receive 1st line therapy	23%	2,817	(NICE 2010)
Patients who failed 1st line therapy	50%	**1,413**	(Sculier 2009)

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

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

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

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

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

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

Not applicable.

3.9 Please provide details of the duration of the scheme.

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

3.10 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any

concerns identified during the course of the appraisal? If so, how have these been addressed?

Not applicable.

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

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

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

Not applicable.

4 Cost effectiveness

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

Not applicable.

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

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

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

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

As highlighted in our response to the ACD, BMS maintain that the ERG's survival extrapolation is not a reasonable interpretation of the available clinical evidence and clinical expert opinion. We believe in our extrapolations but recognise that today there is uncertainty in the long term benefit and

therefore, we have presented a base-case which is based on a pragmatic "meet in the middle" approach to OS survival.

In base case (BMS assumptions) below, we have used the BMS preferred assumptions (log-normal OS extrapolation, TTD to model outcomes and costs, utilities from Checkmate 057 with PD adjusted for end of life, BMS nintedanib comparison) and in addition to the 'nivolumab discount' we have applied a 2-year clinical stopping rule and an adjustment for dose intensity (justification of these is provided below).

In base-case (AC assumptions), we present the model with the Appraisal Committee's preferred assumptions, based on the ERG model (exponential OS extrapolation, PFS used for outcomes, TTD for costs, utility value for PD midway between the ERG and BMS estimates, utility value for PFS in line with the Checkmate 057 data, ERG nintedanib comparison). The 'nivolumab discount is applied along with a 2-year clinical stopping rule and an adjustment for dose intensity.

With these changes, in base case analysis with BMS assumptions, the ICER for nivolumab compared with docetaxel is [redacted] per QALY gained. In this revised base-case analysis with AC assumptions, the ICER for nivolumab compared with docetaxel is [redacted].

The results of the analysis without the clinical stopping rule and dose intensity adjustment are presented in Scenario 1 and 2 below.

Support for use of a clinical stopping rule

The patients enrolled in Phase III trials described in Checkmate 017 and 057 demonstrating the clinical efficacy and safety of nivolumab monotherapy in pre-treated advanced NSCLC patients who continued to receive study drug until their disease progressed, or they experienced unacceptable toxicity, as per protocol (p73, section 4.7 of the CS). UK and international expert clinical opinion has confirmed that for those patients who have responded to nivolumab, treat to progression will not be reasonable in routine clinical practice, and that stopping therapy at an appropriate time point should be

considered. Based on available data from BMS' Phase I study Checkmate 003 (CA209-003), looking at various doses of nivolumab across a range of tumour types, including pre-treated advanced NSCLC, UK clinicians agreed that limiting the maximum duration of treatment could be supported. Checkmate 003 had a protocol specified stopping rule for discontinuation of therapy at 96 weeks (1.8 years). The majority of patients (6/7) who achieved complete or partial response before 96 weeks, maintained their response. This treatment pattern is confirmed across all tumour types and all doses of nivolumab in Checkmate 003.

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

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. This was acknowledged in the recent TA 384 (nivolumab for treating advanced [unresectable or metastatic] melanoma), in which the institute noted uncertainty of optimal duration of treatment, and commitment to re-review the evidence in two years when it may be more feasible to clarify optimal duration of treatment. Furthermore, another anti-PD1, pembroluzimab currently under NICE appraisal in NSCLC has suggested stopping anti-PD1 at 2 years regardless of progression status, as discussed at the appraisal committee meeting on 29 June, suggesting that treatment to progression will not be the norm for these products in clinical practice.

We have therefore provided modelling for 2 years of treatment (see also Scenario 4 in the CS, described from page 234-235) to represent real world clinical practice until clarity can be provided.

Support for use of a dose intensity adjustment

Increasing evidence suggests that patients receiving IV medications on a regular treatment schedule, rarely receive all of the planned doses. With the nivolumab dosing schedule (IV every 2 weeks), if a dose is delayed by more than ten days, in reality it is likely to be missed and the patient will progress directly to the next planned dose. In recent health technology assessments for immuno-oncologics, adjustments for dose intensity have been applied to drug costs (for example pembrolizumab in NSCLC [ID 840] and nivolumab in renal cell carcinoma [ID 853]) applied in the economic models.

The proportion of planned nivolumab doses received has been calculated from CheckMate 057 patient-level data as [redacted]%, accounting for the proportion of doses delayed by more than 10 days ([redacted]%), and the proportion of doses omitted ([redacted]%). Similarly, the proportion of planned docetaxel doses in CheckMate 057 was calculated as [redacted]%, accounting for the proportion of doses delayed by more than 10 days ([redacted]%), and the proportion of doses omitted ([redacted]%). As nintedanib is a daily oral treatment, it will not be subject to the same restrictions in terms of missed doses, therefore the intensity of nintedanib was assumed to be 100%, and that of docetaxel (in combination with nintedanib) was assumed to be [redacted]% in line with CheckMate 057.

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

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

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

Not applicable

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

Not applicable

Summary results

Base-case analysis

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

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

A suggested format is shown below (Table 1).

The results of the base-case analyses are provided in Tables 2 and 3.

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

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

	Nivolumab	Docetaxel	Nintedanib
Intervention cost (£)	[redacted]	[redacted]	[redacted]
Treatment administration (£)	2,609	1,108	1,119
Treatment monitoring costs (£)	1,149	697	705
PF cost (£)	2,923	1,439	1,456
PD cost (£)	15,076	12,580	16,382
AE costs (£)	332	1,247	992
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)(nivolumab-comparator)	-	[redacted]	[redacted]
LYG	2.09	1.32	1.79
LYG difference (nivolumab – comparatorl)	-	0.76	0.30
QALYs	1.29	1.32	1.79
QALY difference (nivolumab – comparatorl)		0.49	0.22
ICER (£; nivolumab vs. comparator)	-	[redacted]	[redacted]

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

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

	Nivolumab	Docetaxel	Nintedanib
Intervention cost (£)	[redacted]	[redacted]	[redacted]
Treatment administration (£)	2,398	909	1,563
Treatment monitoring costs (£)	1,047	542	1,007
PF cost (£)	2,928	1,789	2,078
PD cost (£)	11,140	9,687	12,518
AE costs (£)	332	1,247	992
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)(nivolumab-comparator)	-	[redacted]	[redacted]
LYG	1.81	1.07	1.46
LYG difference (nivolumab – comparatorl)	-	0.73	0.35
QALYs	0.97	0.62	0.86
QALY difference (nivolumab – comparatorl)		0.35	0.11
ICER (£; nivolumab vs. comparator)	-	[redacted]	[redacted]

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

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

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

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in Table 2.

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

Table 2: Base-case incremental results (BMS assumptions)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Nivolumab	[redacted]	[redacted]	1.29				
Docetaxel	[redacted]	[redacted]	0.80	[redacted]	0.76	0.49	[redacted]
Nintedanib	[redacted]	[redacted]	1.07	[redacted]	0.30	0.22	[redacted]

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

Table 5: Base-case incremental results (AC assumptions)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Nivolumab	[redacted]	[redacted]	0.97				
Docetaxel	[redacted]	[redacted]	0.62	[redacted]	0.73	0.35	[redacted]
Nintedanib	[redacted]	[redacted]	0.86	[redacted]	0.35	0.11	[redacted]

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

The base-case comparator in the model is docetaxel. Docetaxel is the current standard of care in pre-treated patients with squamous NSCLC in the UK and is the treatment likely to be displaced by the introduction of Nivolumab. Nintedanib in combination with docetaxel was approved by NICE for patients with adenocarcinoma in 2015. Use in this indication is currently low, and there are limited data to allow an appropriate indirect comparison with nivolumab and therefore results of the comparison with nintedanib are uncertain and should be interpreted with caution.

Sensitivity analyses

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

Deterministic sensitivity analysis was undertaken by varying cost, utility and efficacy parameters by their confidence intervals or ±20% based on data availability. The results are presented in Table to 9 and in Figures 1-4 below.

Table 6: Results of deterministic sensitivity analysis vs docetaxel (BMS assumptions)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 1: Tornado diagram vs docetaxel (BMS assumptions)

Table 7: Results of deterministic sensitivity analysis vs nintedanib (BMS assumptions)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Efficacy				
HR on PFS - nintedanib	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
HR on OS - nintedanib	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 2: Tornado diagram vs nintedanib (BMS assumptions)

Table 8: Results of deterministic sensitivity analysis vs docetaxel (AC assumptions)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 3: Tornado diagram vs docetaxel (AC assumptions)

Table 9: Results of deterministic sensitivity analysis vs nintedanib (AC assumptions)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Efficacy				
HR on PFS - nintedanib	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
HR on OS - nintedanib	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 4: Tornado diagram vs nintedanib (AC assumptions)

[redacted]

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

Results of the probabilistic sensitivity analysis (PSA) on the PAS are shown in Tables 10 and 11 below. Using the BMS assumptions, the PSA ICER vs docetaxel is [redacted] per QALY gained. Using the AC assumptions, the PSA ICER vs docetaxel is [redacted] per QALY gained The PSA was run for 1000 iterations and the cost-effectiveness scatter plots are shown in Figures 5 to 8.

Table 10: Probabilistic results (BMS assumptions)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	1.29			
Docetaxel	[redacted]	0.81	[redacted]	0.48	[redacted]
Nintedanib	[redacted]	1.07	[redacted]	0.22	[redacted]

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

Table 11: Probabilistic results (AC assumptions)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	0.97			
Docetaxel	[redacted]	0.63	[redacted]	0.34	[redacted]
Nintedanib	[redacted]	0.86	[redacted]	0.11	[redacted]

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

Figure 5: Cost-effectiveness plane for nivolumab vs. docetaxel (BMS assumptions)

Figure 6: Cost-effectiveness plane for nivolumab vs. nintedanib (BMS assumptions)

Figure 7: Cost-effectiveness plane for nivolumab vs. docetaxel (AC assumptions)

Figure 8: Cost-effectiveness plane for nivolumab vs. nintedanib (AC assumptions)

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

In these analyses, the simple discount has been used but without the stopping rule or dose intensity discount. In Scenario 1, the BMS assumptions are used and in Scenario 2 the AC assumptions.

Finally, we are aware that the utilities we have applied in the “AC assumptions” model are slightly different to those that were used in the squamous submission (squamous PD = 0.592, PFS = 0.7500). The values presented here are slightly lower, in line with those in the CheckMate 057 for PFS (0.713) and taking a mid-value between the CheckMate 057 value and the ERG preferred value for PFS (0.657). As the NSCLC histology was different between the two assessments, we consider it is plausible that utilities would vary slightly, but have presented the results of the AC assumptions analysis if the squamous utilities are applied in Scenario 3. This shows that the impact on the ICERs is minimal.

Scenario 1: BMS assumptions with 'nivolumab discount' and no other adjustments

Table 12: Scenario 1 - Summary of QALY gain by health state vs docetaxel

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.53	0.26	0.27	0.27	55.0%
PD	0.77	0.60	0.17	0.17	34.9%
AE disutility	-0.01	-0.06	0.05	0.05	10.1%
Total	1.29	0.80	0.49	0.49	100.0%

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

*No utility is assigned to the death state

Table 13: Scenario 1 - Summary of QALY gain by health state vs nintedanib

Health state	Nivolumab QALY	NIntedanib QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.53	0.26	0.27	0.27	122.7%
PD	0.77	0.85	-0.08	0.08	38.4%
AE disutility	-0.01	-0.04	0.03	0.03	15.7%
Total	1.29	1.07	0.22	0.22	100.0%

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

*No utility is assigned to the death state

Table 14: Scenario 1 - Summary of costs vs. docetaxel

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,203	1,108	2,095	2,095	7.0%
Monitoring cost	1,416	697	719	719	2.4%
AEs	332	1,247	-915	915	3.1%

Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 15: Scenario 1 - Summary of costs vs. nintedanib

Health state	Nivolumab cost (£)	Nintedanib cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,203	1,119	2,084	2,084	12.9%
Monitoring cost	1,416	705	711	711	4.4%
AEs	332	992	-660	660	4.1%
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 16: Scenario 1 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	[redacted]	1.29			
Docetaxel	[redacted]	0.80	[redacted]	[redacted]	[redacted]
Nintedanib	[redacted]	1.07	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: Quality-Adjusted Life Year

Table 17: Results of deterministic sensitivity analysis vs docetaxel (Scenario 1)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Table 18: Results of deterministic sensitivity analysis vs nintedanib (Scenario 1)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Efficacy				
HR on PFS - nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
HR on OS - nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 9: Tornado Diagram versus docetaxel (Scenario 1)

Figure 10: Tornado Diagram versus nintedanib (Scenario 1)

Table 19: Probabilistic results (Scenario 1)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	1.29			
Docetaxel	[redacted]	0.81	[redacted]	0.48	[redacted]
Nintedanib	[redacted]	1.07	[redacted]	0.22	[redacted]

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

Figure 11: Cost-effectiveness plane for nivolumab vs. docetaxel (Scenario 1)

Figure 12: Cost-effectiveness plane for nivolumab vs. nintedanib (Scenario 1)

Scenario 2: AC assumptions with 'nivolumab discount' and no other adjustments

Table 20: Scenario 2 - Summary of QALY gain by health state vs docetaxel

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.53	0.32	0.21	0.21	59.6%
PD	0.45	0.36	0.09	0.09	26.2%
AE disutility	-0.01	-0.06	0.05	0.05	14.2%
Total	0.97	0.62	0.35	0.35	100.0%

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

*No utility is assigned to the death state

Table 21: Scenario 2 - Summary of QALY gain by health state vs nintedanib

Health state	Nivolumab QALY	Nintedanib QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.53	0.38	0.15	0.15	138.7%
PD	0.45	0.53	-0.08	0.08	-69.5%
AE disutility	-0.01	-0.04	0.03	0.03	30.7%
Total	0.97	0.86	0.11	0.11	100.0%

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

*No utility is assigned to the death state

Table 22: Scenario 2 - Summary of costs vs. docetaxel

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,363	909	2,455	2,455	8.2%
Monitoring cost	1,481	542	939	939	3.1%
AEs	332	1,247	-915	915	-3.1%

Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 23: Scenario 2 - Summary of costs vs. nintedanib

Health state	Nivolumab cost (£)	Nintedanib cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,363	1,563	1,801	1,801	15.5%
Monitoring cost	1,481	1,007	475	475	4.1%
AEs	332	992	-660	660	5.7%
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 24: Scenario 2 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	[redacted]	0.97			
Docetaxel	[redacted]	0.62	[redacted]	[redacted]	[redacted]
Nintedanib	[redacted]	0.86	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: Quality-Adjusted Life Year

Table 25: Results of deterministic sensitivity analysis vs docetaxel (Scenario 2)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Table 26: Results of deterministic sensitivity analysis vs nintedanib (Scenario 2)

Parameter	Analysis	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case analysis		[redacted]	[redacted]	[redacted]
Discount rate - costs	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Discount rate - outcomes	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Average body weight	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
BSA	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Costs				
Cost - PF state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Cost - PD state	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Terminal cost	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Administration cost – docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost – nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Monitoring cost - docetaxel	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Outcomes				
Utility weight, PFS	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Utility weight, PD	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
Efficacy				
HR on PFS - nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]
HR on OS - nivolumab	Lower	[redacted]	[redacted]	[redacted]
	Higher	[redacted]	[redacted]	[redacted]

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

Figure 13: Tornado Diagram versus docetaxel (Scenario 2)

Figure 14: Tornado Diagram versus nintedanib (Scenario 2)

Table 27: Probabilistic results (Scenario 2)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	0.97			
Docetaxel	[redacted]	0.63	[redacted]	0.34	[redacted]
Nintedanib	[redacted]	0.86	[redacted]	0.11	[redacted]

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

Figure 15: Cost-effectiveness plane for nivolumab vs. docetaxel (Scenario 2)

Figure 16: Cost-effectiveness plane for nivolumab vs. nintedanib (Scenario 2)

Scenario 3: AC assumptions except utility – squamous values used, with 'nivolumab discount', dose cap and dose intensity adjustment

Table 28: Scenario 3 - Summary of QALY gain by health state vs docetaxel

Health state	Nivolumab QALY	Docetaxel QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.54	0.33	0.21	0.21	59.7%
PD	0.46	0.36	0.09	0.09	26.3%
AE disutility	-0.01	-0.06	0.05	0.05	14.0%
Total	0.99	0.63	0.35	0.35	100.0%

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

*No utility is assigned to the death state

Table 29: Scenario 3 - Summary of QALY gain by health state vs nintedanib

Health state	Nivolumab QALY	Nintedanib QALY	Incremental QALYs	Absolute incremental QALYs	% absolute incremental QALYs
PF	0.54	0.38	0.16	0.16	139.6%
PD	0.46	0.54	-0.08	0.08	-70.1%
AE disutility	-0.01	-0.04	0.03	0.03	30.5%
Total	0.99	0.87	0.11	0.11	100.0%

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

*No utility is assigned to the death state

Table 30: Scenario 3 - Summary of costs vs. docetaxel

Health state	Nivolumab cost (£)	Docetaxel cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	2,398	909	1,490	1,490	7.6%
Monitoring cost	1,047	542	505	505	2.6%
AEs	332	1,247	-915	915	4.7%
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 31: Scenario 3 - Summary of costs vs. nintedanib

Health state	Nivolumab cost (£)	Nintedanib cost (£)	Incremental costs (£)	Absolute incremental costs (£)	% absolute incremental costs
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	2,398	1,563	836	836	63.7%
Monitoring cost	1,047	1,007	41	41	3.1%
AEs	332	992	-660	660	-50.3%%
Total treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

Table 32: Scenario 3 - Cost-effectiveness analysis

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Nivolumab	[redacted]	0.99			
Docetaxel	[redacted]	0.63	[redacted]	[redacted]	[redacted]
Nintedanib	[redacted]	0.87	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: Quality-Adjusted Life Year

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

The PAS is not dependent on any clinically variable parameters.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 33). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 33: Results showing the impact of patient access scheme on ICERs for scenarios

ICERs	**Nivolumab vs. docetaxel**		**Nivolumab vs. nintedanib**	
	Without PAS	With PAS	Without PAS	With PAS
Base-case (BMS assumptions)	£81,171	[redacted]	[redacted]	[redacted]
Base-case (AC assumptions	£101,081	[redacted]	[redacted]	[redacted]
Scenario 1: BMS assumptions without stopping rule or dose intensity adjustment	£106,653	[redacted]	[redacted]	[redacted]
Scenario 2: AC assumptions without stopping rule or dose intensity adjustment	£153,883	[redacted]	[redacted]	[redacted]
Scenario 3: Basecase with AC assumptions, except utility	£99,747	[redacted]	[redacted]	[redacted]

PAS: patient access scheme.

4.14 Appendix A: Additional documents

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

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

4.15 Appendix B: Details of outcome-based schemes

Not applicable

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

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

Response

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

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

Response

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

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

Response

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

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

Response

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

Response

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

Response

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

Response

4.15.8 Please present the cost-effectiveness results as follows.

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

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

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

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