Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer [ID1249]

Single Technology Appraisal

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

Type of stakeholder:

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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Company	Bristol Myers-Squibb	**Evidence requested by NICE: ATTRACTION-3 August 2020 database lock** As requested in the Appraisal Consultation Document, additional evidence is provided from the ATTRACTION-3 [redacted] database lock (data cut-off: [redacted]), reporting a minimum follow-up of [redacted] (Table 1). These results remain consistent with the results of the primary analysis presented in the company submission. As can be expected, median outcomes and outcomes at one year were [redacted]. However, outcomes in the nivolumab arm continued to demonstrate [redacted] OS rates at 24 months [redacted] and 36 months ([redacted]) compared with the chemotherapy control. **Table 1. ATTRACTION-3 updated outcomes** [table not reproduced here] **Figure 1. ATTRACTION-3: Kaplan-Meier Plot of Overall survival - [redacted]** [Figure redacted] **Figure 2. ATTRACTION-3: Kaplan-Meier Plot of progression-free survival - [redacted]** [Figure redacted]	The new 36-month follow-up data from the ATTRACTION-3 trial was taken into consideration at the 2nd committee meeting. (see FAD section 3.4).

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2	Company	Bristol Myers-Squibb	**Has all the relevant evidence been taken into account?** Since publication of the Appraisal Consultation Document, additional evidence has been sought and further economic evaluations have been undertaken in order to address the Committee's requests. This includes: • Data describing additional follow-up in ATTRACTION-3 • Economic evaluations applying the Committee's preferred assumptions and modelling methods or addressing the Committee's stated concerns. • Economic evaluations using the data describing additional follow-up from ATTRACTION-3. In light of the updates to the evidence base, the Committee has not yet reviewed all relevant evidence; however, this will be remedied following receipt of the evidence contained in this report.	Comment noted. The additional follow-up data from ATTRACTION-3 and updated economic evaluations were taken into account at the 2nd committee meeting.

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3	Company	Bristol Myers-Squibb	**Are the summaries of clinical and resource savings reasonable interpretations of the evidence?** BMS does not believe that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence, as detailed below. **3.1. Clinical benefits** **3.1.1. Survival benefit** Although there is initial crossover in the OS Kaplan-Meier data, median OS and OS rates from 6 months to end of follow up show a beneficial impact for nivolumab versus taxanes. Landmark analyses (**Figure 5**) demonstrate that outcomes are significantly improved for nivolumab versus taxanes in those patients alive at three months. As noted by clinical experts in the Appraisal Consultation Document, this is a common pattern of response for immuno-oncology therapies, particularly those indications where survival is short and evidence is versus an active comparator. This is because of the delay in benefit as the immune system is activated, while chemotherapy immediately acts on the cancer cells. However, it is clear that nivolumab is associated with significant survival benefits across the population of patients with oesophageal squamous cell carcinoma. Immunotherapies such as nivolumab have a different mechanism of action than conventional anti-cancer therapies, which typically aim to reduce the tumour burden through direct disruption of tumour cell proliferation or induction of apoptosis. By contrast, immunotherapy agents such as nivolumab, often have a delayed clinical responses[2] and differences in response patterns after immunotherapy may potentially be prematurely misclassified as disease progression under the WHO or RECIST criteria.[2, 3] For the same reasons, PFS may not be an adequate endpoint in immunotherapy trials and may not be considered a surrogate for OS for the achievement of clinical efficacy. The Appraisal Consultation Document suggests that most of the overall survival benefit from nivolumab was after progression. However, it should be noted that there is significant survival benefit both before and after progression. As demonstrated in **Figure 3** and **Figure 4**, nivolumab improves pre and post-progression survival versus taxanes. In the pre-progression setting, OS is [redacted] at 36 months for nivolumab versus [redacted] in the control arm, while in the post-progression setting, OS at 12 months is [redacted] for nivolumab versus [redacted] for taxanes.	Comment noted. The committee noted the improved OS and PFS data for nivolumab compared with taxanes based on the updated data cut. However, there remains an increased risk of dying in the first 3 months compared with taxane therapy. The committee concluded that nivolumab improves overall survival despite a greater death rate in the first 3 months. See FAD 'why the committee made these recommendations' and section 3.5.

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			Figure 3. ATTRACTION-3 pre-progression survival [Figure redacted] **Figure 4. ATTRACTION-3 post-progression survival** [Figure redacted] **Figure 5. ATTRACTION-3 landmark analysis based on patients alive at three months** [Figure redacted]	
4	Company	Bristol Myers-Squibb	**Extension to life** When considering application of end-of-life criteria, the committee concluded that nivolumab was indicated for people with a short life expectancy and considered it likely that the extension to life criterion was met but would like to see the effect of the 36-month data on modelled survival benefit. It should be noted that there was [redacted] on median survival outcomes, with a median overall survival benefit of [redacted] months in the [redacted] database lock. However, the additional follow-up was sufficient to demonstrate that end of life criteria was met in terms of at least three months of additional survival based on restricted mean OS ([redacted] months for nivolumab for [redacted] months for taxanes). Based on the data provided in the company submission, the observed median overall survival benefit with nivolumab of 2.5 months was extrapolated. This gave an expected overall mean survival benefit of 7.8 months in the submission base case model and 4.0 months in the ERG model. Based on additional follow-up, this mean survival benefit was extended to [redacted].	Comment noted. The committee considered that the extension-to-life criterion was met based on the trial data (see FAD section 3.13).
5	Company	Bristol Myers-Squibb	**Hospitalisation cost** Based on the clinician survey detailed in the company submission, the model assumes that disease management requires a mean of 0.095 hospitalisations per week. However, the hospitalisation cost is derived from NHS National Cost Collection based on a weighted mean of hospitalisation costs, which have a length of stay ranging from 3 days (cost: £1,907) to 19 days (cost: £8,986). This cost is applied on a weekly basis, raising an implausible scenario where the weekly cost incurred is appropriate for a period of time longer than a week.	Comment noted. The committee acknowledged that the clinicians' survey gave a value for how often people would be admitted into hospital, but not how long they would have to stay there. The committee concluded that the cost of hospitalisation remains an uncertainty that has a substantial effect on the ICER, and that the company had not given adequate justification for estimate of hospital costs based on stay duration of 1 bed day (see section 3.11).

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6	Company	Bristol Myers-Squibb	**Utility values** The Committee considered it plausible for the utility before progression for nivolumab to be higher than the taxane arm, based on differences in tolerability and adverse events. Further, the Committee concluded that most of the overall survival benefit from nivolumab was after progression. However, the Committee concluded that the company had not given adequate justification for a long-term difference in utility after progression. As utility in oncology is typically a function of time to death, improved OS rates are a key component in postponing quality of life decrements. The Appraisal Consultation Document suggests that most of the overall survival benefit from nivolumab was after progression. Hence, it is appropriate to reflect this benefit in the post-progression utility value. Further, patients in the nivolumab arm frequently continued receiving nivolumab following progression, as noted in the ERG report. Hence, any beneficial impact associated with nivolumab treatment is continued into the post-progression state for those patients. Pooling post-progression quality of life data assumes that patients in the taxane arm receive benefit equivalent to patients receiving nivolumab. Additional analysis is presented in the appendix to this response, demonstrating that benefit can be stratified by treatment status, rather than by progression status. This is limited by poor data collection when off treatment. However, it demonstrates that treatment status may be a more reliable predictor of benefit than progression status.	Comment noted. Based on differences in tolerability and adverse events, the committee considered it plausible that the utility before progression for nivolumab was higher than for taxanes but the size of the difference was likely to have been overestimated by the company. Post-progression utility in the short term could be higher on nivolumab than taxanes, due to spill over of toxic effects. However, follow-on treatment after nivolumab therapy may influence utility causing it to fluctuate over time. The committee concluded that it was unlikely for utility to be higher with nivolumab for the whole duration from progression to patient death. It considered it more plausible that post-progression utility would be the same for nivolumab and taxane therapy (see section 3.10).
7	Company	Bristol Myers-Squibb	**Impact of subsequent therapies** As noted in the ERG report, subsequent therapy (i.e. not allocated study therapy) was received by 119 (57%) of 210 patients in the nivolumab group and 115 (55%) of 209 patients in the taxanes group.[4] However, it should be noted that this has limited impact on survival outcomes, as demonstrated in Figure 6, as censoring patients who receive subsequent therapy does not greatly impact the comparison between nivolumab and taxanes. **Figure 6. ATTRACTION-3: Overall survival censored for subsequent therapy** [Figure redacted]	Comment noted. The committee accepted that third-line therapy does not greatly affect the relative OS of nivolumab compared with taxane therapy (see section 3.10).
8	Company	Bristol Myers-Squibb	**Are the recommendations sound and a suitable basis for guidance to the NHS?** BMS does not believe that the recommendations can be considered sound and a suitable basis for guidance to the NHS. A thorough discussion of the Appraisal Committee recommendations and Appraisal Consultation Document has been provided above, primarily, this response outlines additional clinical and economic evidence that can be used to support decision-making. Thus, the recommendations made within the Appraisal Consultation Document should be reviewed in the light of this evidence.	Comment noted. The recommendations made by the committee considered all the available evidence.

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9	Company	Bristol Myers-Squibb	**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?** The Committee recognised that there is a significant unmet need in patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose disease has progressed after fluoropyrimidine and platinum-based combination therapy. Further, the Committee noted that it disproportionately affects people from lower socioeconomic backgrounds. As noted in the company submission, the incidence of oesophageal cancer is strongly correlated to age, where around 41% of new cases in the UK between 2014 to 2015 were diagnosed in those over 75 years old.[5] In addition, the five-year net survival of oesophageal cancer patients aged 70 years and over is notably poorer compared with younger patients, particularly in female patients. Nivolumab provides a treatment option with proven efficacy and tolerability, with the potential to impact on symptoms, progression and survival. Ageing well and tackling premature mortality is a priority for NHS England.[6]	Comment noted. The committee acknowledged that the incidence of oesophageal cancer is higher in elderly patients and prognosis is poorer. However, it is not possible to consider differences in the prevalence of oesophageal squamous cell carcinoma in a technology appraisal. No further equality issues were identified by NICE for this appraisal.
10	Company	Bristol Myers-Squibb	**Survival extrapolation** Based on the ATTRACTION-3 [redacted] database lock, it can be observed that both the company and ERG base case analysis underestimated long-term overall survival outcomes for nivolumab and taxanes (Table 2). As these values are underestimated, it is necessary to assess the impact of using the updated ATTRACTION-3 data to inform cost-effectiveness outcomes. Using the methodology outlined in the company submission, patient-level data from the ATTRACTION-3 [redacted] database lock were used to inform long-term extrapolations. In line with preferences stated by the ERG, the patient-level data was assessed using a semi-parametric fit, applying Kaplan-Meier data until 5.75 months followed by parametric extrapolation. **Table 2. Comparison of previously predicted overall survival outcomes versus observed outcomes from ATTRACTION-3 [redacted] database lock** [Table not reproduced here]	Comment noted. The committee noted that overall survival benefit seen at 36 months was consistent with the 24-month follow-up data.

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11	Company	Bristol Myers-Squibb	**Overall survival** In order to model OS in the nivolumab arm, Kaplan-Meier data was applied until 25 weeks followed by parametric extrapolation using the log-logistic distribution to provide an appropriate fit. This approach predicted a median OS of 47.0 weeks and a mean OS of 170.4 weeks. When assessing the Akaike and Bayesian Information Criteria (AIC and BIC, respectively), the log-logistic distribution provided the best goodness-of-fit, indicating it had a strong fit to the data, whilst this was also supported by a strong visual fit to the data, capturing the hazard of the tail of the Kaplan-Meier. The Gompertz function can be excluded due to implausibly long survival and the exponential function provided a visibly poor fit to the data. Similar to the nivolumab arm, Kaplan-Meier data was applied until 25 weeks for the taxane arm; however, a Weibull distribution followed for the extrapolation period. The Weibull distribution provided a clinically plausible estimation of the mean OS (59.0 weeks), whilst also providing a reasonable goodness-of-fit to the data. Fits predicting mean OS greater than 104 weeks were considered implausible based on clinical expert opinion. **Figure 7. ATTRACTION-3 [redacted] database lock: nivolumab OS** [Figure redacted] **Figure 8. ATTRACTION-3 [redacted] database lock: taxane OS** [Figure redacted]	Comment noted. The estimated overall survival from the company's updated base-case was used by the committee for decision making. It noted that the had not had the opportunity to critique each extrapolation to determine the most appropriate method for each arm or calculate how the selected extrapolations affected the cost effectiveness of nivolumab. The committee concluded that there is substantial uncertainty over the most appropriate method of extrapolating overall survival in the nivolumab and taxane arm.

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12	Company	Bristol Myers-Squibb	**Progression-free survival** In order to model PFS in the nivolumab arm, Kaplan-Meier data was applied until 25 weeks followed by parametric extrapolation using the log-normal distribution to provide an appropriate fit. This approach predicted a median PFS of 7.3 weeks and a mean PFS of 44.0 weeks. When assessing the AIC and BIC, the log-normal distribution provided the best goodness-of-fit from the plausible distributions (log-logistic and gompertz distributions are deemed implausible), indicating it had a strong fit to the data, whilst this was also supported by a strong visual fit to the data. Similar to the nivolumab arm, Kaplan-Meier data was applied until 25 weeks for the taxane arm, however, a Weibull distribution followed for the extrapolation period. The Weibull distribution provided a clinically plausible estimation of the mean PFS (22.9 weeks), whilst also providing a strong fit to the data via the goodness-of-fit statistics. **Figure 9. ATTRACTION-3 [redacted] database lock: nivolumab PFS** [Figure redacted] **Figure 10. ATTRACTION-3 [redacted] database lock: taxane PFS** [Figure redacted]	Comment noted. The committee accepted that extrapolation of progression-free survival did not have a significant impact on the ICER.
13	Company	Bristol Myers-Squibb	**Time on treatment** In order to model time on treatment in the nivolumab arm, Kaplan-Meier data was applied until 25 weeks followed by parametric extrapolation using the Weibull distribution to provide an appropriate fit. This approach predicted a median time on treatment of 11.1 weeks and a mean time on treatment of 25.3 weeks. When assessing the AIC and BIC statistics, the Weibull distribution a reasonable goodness-of-fit, whilst this was also supported by a strong visual fit to the data. Similar to the nivolumab arm, Kaplan-Meier data was applied until 25 weeks for the taxane arm, however, a log-logistic distribution followed for the extrapolation period. The log-logistic distribution provided a clinically plausible estimation of the mean time on treatment (16.3 weeks), whilst also providing a reasonable goodness-of-fit to the data. **Figure 11. ATTRACTION-3 [redacted] database lock: nivolumab time on treatment** [Figure redacted] **Figure 12. ATTRACTION-3 [redacted] database lock: taxane time on treatment** [Figure redacted]	Comment noted. The estimated time on treatment from the company's updated base-case was used by the committee for decision making.

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14	Company	Bristol Myers-Squibb	**Drug costs** In line with stated preferences in the Appraisal Consultation Document, drug costs in the model have been updated to use eMIT.	Comment noted.
15	Company	Bristol Myers-Squibb	**Utility values** The Committee considered it plausible for the utility before progression for nivolumab to be higher than the taxane arm, based on differences in tolerability and adverse events. Further, the Committee concluded that most of the overall survival benefit from nivolumab was after progression. However, the Committee concluded that the company had not given adequate justification for a long-term difference in utility after progression. As utility in oncology is typically a function of time to death, improved OS rates are a key component in postponing quality of life decrements. Further, patients in the nivolumab arm frequently continued receiving nivolumab following progression, as noted in the ERG report. Hence, any beneficial impact associated with nivolumab treatment is continued into the post-progression state for those patients. Pooling post-progression quality of life data assumes that patients in the taxane arm receive benefit equivalent to patients receiving nivolumab. Additional analysis was undertaken to assess the impact of treatment status on quality of life. Using a mixed effects model, as per ERG preference, data were stratified by treatment status. Collection of data was notably poorer in the off-treatment setting, leading to increased missing values. Hence, these values should be considered as supportive evidence. However, this clearly demonstrates the impact of treatment status may be greater than the impact of progression status, as demonstrated in Table 6. **Table 3. ATTRACTION-3 utility values by treatment status** [Table not reproduced here]	Comment noted. The committee accepted that in the short-term people having nivolumab would have higher utility than those having taxane therapy, due to continued adverse effects of treatment. However, utility would then fluctuate over time and be dependent on follow-up treatment. The committee concluded that the most plausible scenario was for post-progression utility to be the same for nivolumab and taxane therapy (see FAD section 3.10).

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16	Company	Bristol Myers-Squibb	**Updated base case analysis** The results of the base case analysis are summarised in Table 4. In terms of comparator treatments (taxanes), the model predicts a median OS of 0.690 years, with an accrual of [redacted] discounted QALYs over the modelled time horizon. By comparison, it was predicted that the use of nivolumab will result in an additional 0.512 discounted QALYs (total: [redacted] discounted QALYs) and an additional 0.724 undiscounted life years (total: [redacted] undiscounted life years), respectively. It was estimated that patients receiving nivolumab would spend [redacted] years in the pre-progression health state (versus [redacted] for taxanes), with a subsequent [redacted] years in the post-progression health state (versus [redacted] for taxanes), indicating that nivolumab is associated with incremental benefit across all health states. Total discounted costs associated with nivolumab (with PAS), accrued over the modelled time horizon, were predicted to be £[redacted]. By comparison, total discounted costs associated with taxanes were notably lower, predicted to be £[redacted]. Incremental discounted costs were predicted to be £24,665 over taxanes, under base case assumptions. The resultant ICER estimate for nivolumab versus taxanes was £48,205 per QALY gain. Therefore, the base case ICER is below a £50,000 per QALY wiliness-to-pay threshold when the current nivolumab PAS discount is applied. **Table 4. Base case analysis results (with PAS, lifetime horizon)** [Table not reproduced here]	The committee considered the company's updated base-case analysis and the ERG's updated assumptions (for utilities, administration costs and hospitalisation costs). The ERG administration costs and utilities were considered to be most appropriate. Following the second meeting, the company updated its commercial offer. Taking this into account, nivolumab was considered likely to be cost effective (see FAD section 3.12)

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17	Company	Bristol Myers-Squibb	**Alternative survival extrapolations** In order to assess the impact of alternative parametric fittings on the cost-effectiveness of nivolumab, alternative survival curves based on the updated ATTRACTION-3 data have been applied within the model as scenario analyses. All extrapolations have been assessed for completeness. However, it should be noted that several of these extrapolations are not considered appropriate. Clinically implausible fits are presented in grey italics and are defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible. The impact of applying alternative survival extrapolations for the nivolumab and taxane arms (OS, PFS and time on treatment) is shown in Table 5. Predicted discounted incremental QALYs ranged from 0.409 to 0.512; while PFS extrapolations did not greatly impact on the QALY gains, OS extrapolations had a large impact, with shorter extrapolations reducing survival benefit; conversely, longer extrapolations increasing QALY accrual. There was a similar variation in discounted incremental costs ranging from £22,826 to £28,289. This had an associated impact on ICERs versus taxanes, which ranged between £48,205 per QALY and £56,959 per QALY. **Table 5. Scenario analysis: impact of alternative extrapolations using updated ATTRACTION-3 database lock** [Table not reproduced here]	Comment noted. The committee agreed that alternative extrapolations of PFS did not have a significant impact on the ICER. It concluded that is substantial uncertainty remained regarding extrapolations of overall survival and time on treatment (see FAD section 3.8).

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18	Company	Bristol Myers-Squibb	**Alternative utility values** In order to assess the impact of utility values on the cost-effectiveness of nivolumab, scenario analyses have been undertaken using alternative utility values. Results from the analysis is detailed in Table 6, where application of alternative utilities resulted in ICER estimates ranging between £50,580 per QALY to £59,995 per QALY. **Table 6. Impact of alternative utilities on base case analysis** [Table not reproduced here] Additionally, scenario analyses were undertaken assessing the impact of utility values stratified by initial treatment status. Results from the analysis is detailed in Table 7, where application of alternative utilities resulted in ICER estimates ranging between £46,448 per QALY and £50,042 per QALY. **Table 7. Impact of using on-treatment and off-treatment utilities on base case analysis** [Table not reproduced here]	Comment noted. The committee considered pooled post-progression utility values to be most appropriate (see FAD section 3.10).