NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treating metastatic or unresectable urothelial cancer after platinum-based chemotherapy [ID995]

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

3. **Additional evidence submitted by the company,** Bristol Myers Squibb

4. **Evidence Review Group critique of the additional evidence,** provided by Kleijnen Systematic Reviews

There we no comments submitted from clinical or patient experts, or through the NICE website.

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

Nivolumab for treating locally advanced unresectable or metastatic urothelial carcinoma after platinum-containing chemotherapy

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 Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Bristol-Myers Squibb	Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the ACD for nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995]. We are extremely disappointed that the Appraisal Committee has decided not to recommend nivolumab for this patient group who have a critical unmet need for novel, effective and tolerable treatment options that offer a durable survival benefit at this stage of disease. We hope that the Committee will reconsider the evidence and work with BMS to make nivolumab available for this patient population. A summary of our response to the ACD is provided below: 1. **Approach to modelling long-term survival.** The basis for the Committee's decision relies on the adoption of standard parametric survival analysis in lieu of a response-based modelling approach, which has not only been criticised by previous NICE Committees,[1] but is not supported by the clinical evidence available and does not characterise the survival benefit that can be achieved with immunotherapies such as nivolumab. 2. **Updated survival data from CheckMate 275 and CheckMate 032.** Updated survival data are now available from the CheckMate 275 and 032 trials, providing clinical validation for the long-term survival benefit estimated for nivolumab within the submitted base case economic analysis, and the use of the response-based survival modelling approach. 3. **Application of a two-year treatment stopping rule.** Incorporation of a two-year treatment stopping rule for nivolumab is in line with the mandated treatment stopping rules included within the positive recommendations for nivolumab by NICE in three prior indications.[1-3] We therefore believe such a stopping rule should be considered for nivolumab in this appraisal going forwards and have incorporated such a stopping rule in the revised base case analysis accompanying this response (see below). 4. **Revised BMS base case analysis.** Results from the revised base case analysis incorporating the latest CheckMate 032 data and a two-year clinical stopping rule demonstrate nivolumab to be cost-effective versus	Comment noted. The committee discussed the company's response to the ACD. Please see sections 3.3-3.5, 3.9, and 3.12-3.16 of the final appraisal determination.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the relevant comparators to this appraisal, both when adopting the response-based modelling approach, (ICER range: £23,500 to £28,300 per quality-adjusted life year [QALY] gained), and when using the Evidence Review Group (ERG) and Committee-preferred standard parametric survival modelling approach (ICER range: £41,200 to £54,900 per QALY gained). 5. **Relevance of paclitaxel comparison for UK decision-making.** Paclitaxel is the comparator clearly stated by UK clinical experts to represent standard of care in this indication and the data for this comparator are derived from a recent, UK-based trial. Versus paclitaxel nivolumab is demonstrated to be cost-effective, with an ICER of £28,683 per QALY gained using the revised BMS base case analysis and £41,195 per QALY gained using the ERG-preferred base case analysis (including the standard parametric survival modelling approach). 6. **Further scenarios for validation.** Three further economic analysis scenarios using a piecewise modelling approach and a treatment waning effect are also presented for consistency with the approaches explored within the appraisals for pembrolizumab and atezolizumab in the same indication.[4, 5] Irrespective of the survival modelling approach taken, nivolumab is cost-effective versus the relevant comparators to this appraisal, with ICERs falling below the £50,000 per QALY gained threshold across all three scenarios. Full discussion of the above points is provided within this document. Full results from the latest database locks of CheckMate 275 and CheckMate 032, together with the results of the revised BMS base case analysis and supportive scenario analyses are provided within the accompanying appendix. Taken together, BMS are confident that the results of the revised economic analyses demonstrate nivolumab to be cost-effective when using the Committee and ERG's preferred assumptions (including the standard parametric survival modelling approach), and are well below NICE's cost-effectiveness threshold for end-of-life indications when using the BMS response-based survival modelling approach. BMS welcome the opportunity to present our response to this preliminary recommendation from NICE and hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of nivolumab as a treatment for adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.	
2	Company	Bristol-Myers Squibb	1. **Approach to modelling long-term survival**	Comment noted. The committee discussed the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			BMS would like to respond to the Committee's preference for the standard parametric survival modelling approach, given the Committee's prior concerns with this approach in previous and ongoing technology appraisals. Specifically, in the recent ACD for nivolumab as a treatment for recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy, the Committee were concerned with the applicability of standard parametric curves for estimating survival with immuno-oncology drugs compared with chemotherapy drugs.[1] The Committee also considered that the technical support document from the decision support unit at NICE does not adequately reflect the mechanism of action of immunotherapy treatments and that the advice was published before immunotherapy drugs were available.[1] Again, in the recent ACD for pembrolizumab in locally advanced or metastatic urothelial carcinoma, the Committee and ERG preferred the use of a piecewise modelling approach in lieu of standard parametric survival modelling.[4] The current Committee and ERG-preferred approach for this appraisal is therefore inconsistent with previous appraisals for immuno-oncology therapies. Scenario analyses incorporating a piecewise modelling approach and a treatment waning effect in line with the approaches taken within the recent appraisals for pembrolizumab and atezolizumab in the urothelial carcinoma[4, 5] are presented within the appendix of this response. BMS would also like to respond to the Committee's statement that "5-year survival of people on other immunotherapies is approximately 10%"[6], given there are no 5-year data available from any other immunotherapies in urothelial carcinoma. The only 5-year data available from a PD-L1 inhibitor is that from patients with non-small cell lung cancer, melanoma, or renal cell carcinoma treated with nivolumab in the CheckMate 003 trial, whereby patient survival at 5 years was 16%, 34% and 34%, respectively.[7] Modelled survival extrapolations for pembrolizumab, a PD-1 inhibitor, presented at the recent second Appraisal Committee Meeting for urothelial carcinoma suggested that 5-year survival estimates were between 10–20%, depending on the parametric curve chosen.[8] Finally, BMS would like to reiterate the 5-year survival estimates for paclitaxel within the BMS base case analysis of 3%, which are in line with the 2-3% estimates of the clinical experts consulted as part of the pembrolizumab appraisal.[4] [References not reproduced]	company's approach to modelling long-term survival and concluded that a response-based approach introduced unnecessary complexity in to the modelling of survival. The committee's discussion is summarised in section 3.9 of the FAD.
3	Company	Bristol-Myers Squibb	**Updated survival data from CheckMate 275 and CheckMate 032** BMS acknowledge the limitations arising from the immaturity of the clinical data available for nivolumab in this indication and are therefore pleased to share with the Committee the results of the latest database locks from CheckMate 275 and CheckMate 032. Full results from these database locks are provided within the accompanying appendix.	Comment noted. The committee considered the latest data provided by the company in response to the appraisal consultation document. The committee

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			These updated data provide clinical validation for the long-term survival extrapolations estimated within the submitted base case economic analysis. Indeed, the overall survival (OS) rates observed at 2 years in CheckMate 275 and CheckMate 032 are higher than those estimated within the base case economic analysis submitted to NICE (Table 1). Depicted graphically in Figure 1, the OS Kaplan-Meier data from CheckMate 032 and CheckMate 275 can be seen to begin to plateau at a level above that predicted within the base case economic analysis originally submitted to NICE.	agreed that the updated results were confirmatory of the early data cut considered in the ACD. The committee's discussion is summarised in sections 3.4 and 3.5 of the FAD.

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			Table 1 also provides 5-year survival data for patients treated with nivolumab in the CheckMate 003 trial with advanced non-small cell lung cancer (the indication indicated by UK expert clinicians to represent the most biologically similar carcinoma to bladder cancer, based on the strong link to smoking, the choice of treatment used in clinical practice, and the poor outcomes associated with both diseases without treatment[9]), in addition to melanoma and renal cell carcinoma. The longer-term data from CheckMate 275 and CheckMate 032 provide further supportive evidence for the “plateau” effect that has been demonstrated with nivolumab in other indications from CheckMate 003, and the potential for extended survival in a proportion of patients when treated with this immunotherapy.[10-13]	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>

Table 1: Comparison of overall survival extrapolation in model against observed data

<table>
<tr><th rowspan="2">Data source</th><th rowspan="2">Survival curve</th><th colspan="6">Proportion alive, %</th></tr>
<tr><th>1 year</th><th>1.5 years</th><th>2 years</th><th>3 years</th><th>4 years</th><th>5 years</th></tr>
<tr><td colspan="8">Nivolumab</td></tr>
<tr><td>Model estimates for OS</td><td>Generalised gamma (original base case)</td><td>42.34%</td><td>33.82%</td><td>27.54%</td><td>21.66%</td><td>18.51%</td><td>16.55%</td></tr>
<tr><td>CheckMate 275</td><td>Kaplan-Meier data</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>CheckMate 032</td><td>Kaplan-Meier data</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>CheckMate 003 (NSCLC)</td><td>-</td><td>42%</td><td>-</td><td>24%</td><td>18%</td><td>16%</td><td>16%</td></tr>
<tr><td>CheckMate 003 (Melanoma)</td><td>-</td><td>65%</td><td>-</td><td>47%</td><td>41%</td><td>35%</td><td>34%</td></tr>
<tr><td>Checkmate 003 (RCC)</td><td>-</td><td>71%</td><td>-</td><td>48%</td><td>44%</td><td>38%</td><td>34%</td></tr>
</table>

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; RCC: renal cell carcinoma.Figure 1: Validation of model predictions of OS with nivolumab

Figure 5: Validation of model predictions of OS with nivolumab

FIGURE REDACTED – ACADEMIC IN CONFIDENCE

[References not reproduced]

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</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
4	Company	Bristol-Myers Squibb	**3. Application of a two-year treatment stopping rule** Evidence to support the stopping of treatment after two years for patients who are responding to nivolumab is available from the CheckMate 003 trial, which included a 96-week treatment stopping rule.[14] Ongoing responses after treatment cessation were observed in this trial for both patients with advanced NSCLC and melanoma who had completed 96 weeks of therapy with nivolumab.[14] The application of a two-year treatment stopping rule (at which point 100% of patients cease treatment) has been mandated by NHS England as part of the positive recommendations by NICE in the most recent appraisals for nivolumab as a treatment for metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811], previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900] and recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971].[1-3] A two-year treatment stopping rule has also been considered clinically appropriate by the Committee as part of the ongoing appraisal for pembrolizumab within urothelial carcinoma.[4] Based on the clinical rationale to support the early stopping of treatment with nivolumab, which may in turn provide financial benefits to the NHS by reducing drug costs, a two-year treatment stopping rule (at which point 100% of patients cease treatment) is therefore included within the revised base case analysis for nivolumab in this indication going forwards, and presented within the accompanying appendix. [References not reproduced]	Comment noted. The committee noted the application of a 2-year treatment stopping rule discontinued costs but had no impact on clinical outcomes. It agreed that that a lifetime continued treatment effect was implausible. Therefore, committee concluded that a 2-year treatment stopping rule could not be accepted wit See section 3.12 of the FAD.
5	Company	Bristol-Myers Squibb	**4. Revised BMS base case analysis** Based on the release of the updated results from the latest database lock of CheckMate 032, BMS have included a revised base case analysis within the appendix of this response that incorporates the more mature data available from CheckMate 032. This latest database lock provides longer-term data for nivolumab in this indication for a minimum of two years follow-up. Due to the staggered recruitment for some patients, overall patients have been followed up for approximately three years. This is substantially greater follow-up compared with the minimum of 9 months follow-up provided from the initial database lock (26th March 2016) of the CheckMate 032 trial. *It should be noted that due to time constraints, the updated data from CheckMate 275 have not been incorporated within the revised BMS base case analysis.* The revised base case analysis adopts all aspects of the ERG's preferred base case analysis with the following differences: • Retention of the responder-based survival modelling approach (with individual choice of parametric distribution for responders/non-responders as requested by the ERG at the clarification stage, and updated based on statistical fit with the updated data); • The latest pooled analysis, using the updated data from the CheckMate 032 trial, to generate the survival curves for PFS, OS and TTD; • A treatment stopping rule, based on the assumption that 100% of nivolumab patients will discontinue after two years of treatment, if they haven't discontinued previously. In addition, BMS would like to respond to two of the amendments made by the ERG to the economic model, which we believe have been incorrectly implemented. These have subsequently been corrected within the BMS revised base case analysis:	Comment noted. The committee considered both the company and ERG revised base-case ICERs and alternative scenarios in its decision of a most plausible ICER. The committee agreed that the assumptions incorporated in the ERGs revised base-case were mostly consistent with its preferences. See section 3.14-3.16 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• The approach taken by the ERG to apply a weighting to the patient weight across CheckMate 275 and CheckMate 032 assumes a weighting of 50:50 to both trials. This approach is entirely inconsistent with the incorporation of other trial data within the economic model, e.g. efficacy and quality of life data inputs, which have been weighted across both trials based on trial size. The appropriate average weight across both trials should be 78.69 kg. • The approach taken by the ERG to incorporate missed doses within the economic model is not considered appropriate. The ERG approach does not incorporate the shape of the distribution of dose delays, which included delays of <7 days but also >14 days. The approach taken by BMS included both left- and right-skewed patients to ensure the approach included the average dose delay across all patients, and we would therefore argue that our original approach is more appropriate. Full results of the revised BMS base case analysis are provided within the appendix of this response, and demonstrate nivolumab to be cost-effective versus the relevant comparators in this submission. In addition, results are provided for the ERG and Committee-preferred base case analysis, which includes the changes highlighted above, but uses a standard parametric modelling approach in place of the BMS response-based modelling approach. Even under the ERG and Committee-preferred revised base case analysis, nivolumab represents a cost-effective use of NHS resources for patients in this end-of-life indication.	
6	Company	Bristol-Myers Squibb	**5. Relevance of paclitaxel comparison for UK clinical decision-making** BMS would like to emphasise the feedback from the clinical experts at the Committee meeting for this appraisal, who clearly stated that paclitaxel represents the standard of care in the UK for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.[6] Indeed, paclitaxel was stated to be preferred to docetaxel due to its availability and favourable adverse-effect profile. This was also confirmed as part of the PLUTO trial, the UK-based trial providing evidence for paclitaxel within this appraisal, where the control arm of paclitaxel was chosen specifically on the basis of previously published phase II data and a survey prior to the study that showed paclitaxel to be the most widely used drug in this setting in the UK.[15] The comparison of nivolumab versus paclitaxel therefore represents the most relevant comparison for this appraisal. In this context, BMS would like to highlight to the Committee that the data used for paclitaxel within the economic model is derived from a UK-only, phase III randomised controlled trial, in which paclitaxel was used in accordance with UK clinical practice.[15] The evidence base for paclitaxel that informs the comparison with nivolumab is therefore a robust and highly UK-relevant evidence source to support decision-making within the UK. [References not reproduced]	Comment noted. The committee noted that both docetaxel and paclitaxel had been included in the scope for the appraisal, and it agreed that docetaxel was also an appropriate comparator. See FAD section 3.3.
7	Company	Bristol-Myers Squibb	**6. Further scenarios for validation** As the final part of our response, and to ensure the Committee are provided with a complete set of scenarios upon which to base their decision, BMS have conducted three further scenarios that adopt the same approaches to modelling survival as those explored as part of the ongoing technology appraisal for pembrolizumab and atezolizumab in urothelial carcinoma.[4, 5] These further scenarios include the adoption of a treatment waning effect, implemented at both 3 and 5 years, in addition to a piecewise modelling approach. Full results from these scenarios are presented within the accompanying appendix. All three scenarios demonstrate that, irrespective of the survival modelling approach taken, nivolumab is cost-effective versus the relevant comparators to this appraisal, with ICERs falling below the £50,000 per QALY gained threshold across all three scenarios. Taken	Comment noted. The committee considered all scenarios presented in the company's response to the ACD. The committee noted that piecewise modelling approaches have sufficient evidence to support their

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			together, BMS hope that the Committee will be satisfied that the range of alternative scenarios presented as part of this response demonstrate the plausibility of nivolumab to be a cost-effective use of NHS resources in this indication. [References not reproduced]	suitability for modelling survival, and have shown validity in other appraisals. The committee noted that the scenario analysis exploring treatment waning produced counter-intuitive results. The ICERs dropped below the revised base-case level, implying the comparator treatments were more effective in the long-term. See FAD sections 3.9 and 3.13.
8	Company	Bristol-Myers Squibb	**Conclusion** BMS would like to thank the Committee for considering this additional information in assessing the cost-effectiveness of nivolumab for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy. We would like to highlight that with the additional economic analyses presented within the appendix of this response, nivolumab is shown to be plausibly cost-effective when using the ERG and Committee's preferred assumptions and associated with ICERs well below the cost-effectiveness threshold when using the BMS response-based modelling approach. Therefore, we hope that the Committee will revisit their preliminary decision and in doing so are able to make a positive recommendation regarding nivolumab for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.	Comment noted.

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Level 1A City Tower,
Piccadilly Plaza,
Manchester,
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United Kingdom

9th November 2017

Re: Nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995] – company response to Appraisal Consultation Document (ACD)

Dear Helen,

Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the ACD for nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995]. We are extremely disappointed that the Appraisal Committee has decided not to recommend nivolumab for this patient group who have a critical unmet need for novel, effective and tolerable treatment options that offer a durable survival benefit at this stage of disease. We hope that the Committee will reconsider the evidence and work with BMS to make nivolumab available for this patient population.

A summary of our response to the ACD is provided below:

1. **Approach to modelling long-term survival.** The basis for the Committee's decision relies on the adoption of standard parametric survival analysis in lieu of a response-based modelling approach, which has not only been criticised by previous NICE Committees,[1] but is not supported by the clinical evidence available and does not characterise the survival benefit that can be achieved with immunotherapies such as nivolumab.
2. **Updated survival data from CheckMate 275 and CheckMate 032.** Updated survival data are now available from the CheckMate 275 and 032 trials, providing clinical validation for the long-term survival benefit estimated for nivolumab within the submitted base case economic analysis, and the use of the response-based survival modelling approach.
3. **Application of a two-year treatment stopping rule.** Incorporation of a two-year treatment stopping rule for nivolumab is in line with the mandated treatment stopping rules included within the positive recommendations for nivolumab by NICE in three prior indications.[1-3] We therefore believe such a stopping rule should be considered for nivolumab in this

appraisal going forwards and have incorporated such a stopping rule in the revised base case analysis accompanying this response (see below).

4. **Revised BMS base case analysis.** Results from the revised base case analysis incorporating the latest CheckMate 032 data and a two-year clinical stopping rule demonstrate nivolumab to be cost-effective versus the relevant comparators to this appraisal, both when adopting the response-based modelling approach, (ICER range: £23,500 to £28,300 per quality-adjusted life year [QALY] gained), and when using the Evidence Review Group (ERG) and Committee-preferred standard parametric survival modelling approach (ICER range: £41,200 to £54,900 per QALY gained).

5. **Relevance of paclitaxel comparison for UK decision-making.** Paclitaxel is the comparator clearly stated by UK clinical experts to represent standard of care in this indication and the data for this comparator are derived from a recent, UK-based trial. Versus paclitaxel nivolumab is demonstrated to be cost-effective, with an ICER of £28,683 per QALY gained using the revised BMS base case analysis and £41,195 per QALY gained using the ERG-preferred base case analysis (including the standard parametric survival modelling approach).

6. **Further scenarios for validation.** Three further economic analysis scenarios using a piecewise modelling approach and a treatment waning effect are also presented for consistency with the approaches explored within the appraisals for pembrolizumab and atezolizumab in the same indication.[4, 5] Irrespective of the survival modelling approach taken, nivolumab is cost-effective versus the relevant comparators to this appraisal, with ICERs falling below the £50,000 per QALY gained threshold across all three scenarios.

Full discussion of the above points is provided within this document. Full results from the latest database locks of CheckMate 275 and CheckMate 032, together with the results of the revised BMS base case analysis and supportive scenario analyses are provided within the accompanying appendix.

Taken together, BMS are confident that the results of the revised economic analyses demonstrate nivolumab to be cost-effective when using the Committee and ERG's preferred assumptions (including the standard parametric survival modelling approach), and are well below NICE's cost-effectiveness threshold for end-of-life indications when using the BMS response-based survival modelling approach.

BMS welcome the opportunity to present our response to this preliminary recommendation from NICE and hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of nivolumab as a treatment for adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.

Yours sincerely,

[redacted]

Bristol-Myers Squibb Pharmaceuticals Limited – Response to Appraisal Consultation Document for ID995

Contents

1. Approach to modelling long-term survival

BMS would like to respond to the Committee's preference for the standard parametric survival modelling approach, given the Committee's prior concerns with this approach in previous and ongoing technology appraisals. Specifically, in the recent ACD for nivolumab as a treatment for recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy, the Committee were concerned with the applicability of standard parametric curves for estimating survival with immuno-oncology drugs compared with chemotherapy drugs.[1] The Committee also considered that the technical support document from the decision support unit at NICE does not adequately reflect the mechanism of action of immunotherapy treatments and that the advice was published before immunotherapy drugs were available.[1] Again, in the recent ACD for pembrolizumab in locally advanced or metastatic urothelial carcinoma, the Committee and ERG preferred the use of a piecewise modelling approach in lieu of standard parametric survival modelling.[4] The current Committee and ERG-preferred approach for this appraisal is therefore inconsistent with previous appraisals for immuno-oncology therapies. Scenario analyses incorporating a piecewise modelling approach and a treatment waning effect in line with the approaches taken within the recent appraisals for pembrolizumab and atezolizumab in the urothelial carcinoma[4, 5] are presented within the appendix of this response.

BMS would also like to respond to the Committee's statement that "5-year survival of people on other immunotherapies is approximately 10%"[6], given there are no 5-year data available from any other immunotherapies in urothelial carcinoma. The only 5-year data available from a PD-L1 inhibitor is that from patients with non-small cell lung cancer, melanoma, or renal cell carcinoma treated with nivolumab in the CheckMate 003 trial, whereby patient survival at 5 years was 16%, 34% and 34%, respectively.[7] Modelled survival extrapolations for pembrolizumab, a PD-1 inhibitor, presented at the recent second Appraisal Committee Meeting for urothelial carcinoma suggested that 5-year survival estimates were between 10–20%, depending on the parametric curve chosen.[8] Finally, BMS would like to reiterate the

5-year survival estimates for paclitaxel within the BMS base case analysis of 3%, which are in line with the 2-3% estimates of the clinical experts consulted as part of the pembrolizumab appraisal.[4]

2. Updated survival data from CheckMate 275 and CheckMate 032

BMS acknowledge the limitations arising from the immaturity of the clinical data available for nivolumab in this indication and are therefore pleased to share with the Committee the results of the latest database locks from CheckMate 275 and CheckMate 032. Full results from these database locks are provided within the accompanying appendix.

These updated data provide clinical validation for the long-term survival extrapolations estimated within the submitted base case economic analysis. Indeed, the overall survival (OS) rates observed at 2 years in CheckMate 275 and CheckMate 032 are higher than those estimated within the base case economic analysis submitted to NICE (Table 1). Depicted graphically in Figure 1, the OS Kaplan-Meier data from CheckMate 032 and CheckMate 275 can be seen to begin to plateau at a level above that predicted within the base case economic analysis originally submitted to NICE.

Table 1 also provides 5-year survival data for patients treated with nivolumab in the CheckMate 003 trial with advanced non-small cell lung cancer (the indication indicated by UK expert clinicians to represent the most biologically similar carcinoma to bladder cancer, based on the strong link to smoking, the choice of treatment used in clinical practice, and the poor outcomes associated with both diseases without treatment[9]), in addition to melanoma and renal cell carcinoma. The longer-term data from CheckMate 275 and CheckMate 032 provide further supportive evidence for the “plateau” effect that has been demonstrated with nivolumab in other indications from CheckMate 003, and the potential for extended survival in a proportion of patients when treated with this immunotherapy.[10-13]

Table 1: Comparison of overall survival extrapolation in model against observed data

Data source	Survival curve	Proportion alive, %					
		1 year	1.5 years	2 years	3 years	4 years	5 years
Nivolumab							
Model estimates for OS	Generalised gamma (original base case)	42.34%	33.82%	27.54%	21.66%	18.51%	16.55%
CheckMate 275	Kaplan-Meier data	[redacted]	[redacted]	[redacted]	-	-	-
CheckMate 032	Kaplan-Meier data	[redacted]	[redacted]	[redacted]	-	-	-

CheckMate 003 (NSCLC)	-	42%	-	24%	18%	16%	16%
CheckMate 003 (Melanoma)	-	65%	-	47%	41%	35%	34%
Checkmate 003 (RCC)	-	71%	-	48%	44%	38%	34%

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; RCC: renal cell carcinoma.

Figure 1: Validation of model predictions of OS with nivolumab

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

3. Application of a two-year treatment stopping rule

Evidence to support the stopping of treatment after two years for patients who are responding to nivolumab is available from the CheckMate 003 trial, which included a 96-week treatment stopping rule.[14] Ongoing responses after treatment cessation were observed in this trial for both patients with advanced NSCLC and melanoma who had completed 96 weeks of therapy with nivolumab.[14] The application of a two-year treatment stopping rule (at which point 100% of patients cease treatment) has been mandated by NHS England as part of the positive recommendations by NICE in the most recent appraisals for nivolumab as a treatment for metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811], previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900] and recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971].[1-3] A two-year treatment

stopping rule has also been considered clinically appropriate by the Committee as part of the ongoing appraisal for pembrolizumab within urothelial carcinoma.[4]

Based on the clinical rationale to support the early stopping of treatment with nivolumab, which may in turn provide financial benefits to the NHS by reducing drug costs, a two-year treatment stopping rule (at which point 100% of patients cease treatment) is therefore included within the revised base case analysis for nivolumab in this indication going forwards, and presented within the accompanying appendix.

4. Revised BMS base case analysis

Based on the release of the updated results from the latest database lock of CheckMate 032, BMS have included a revised base case analysis within the appendix of this response that incorporates the more mature data available from CheckMate 032. This latest database lock provides longer-term data for nivolumab in this indication for a minimum of two years follow-up. Due to the staggered recruitment for some patients, overall patients have been followed up for approximately three years. This is substantially greater follow-up compared with the minimum of 9 months follow-up provided from the initial database lock (26th March 2016) of the CheckMate 032 trial. *It should be noted that due to time constraints, the updated data from CheckMate 275 have not been incorporated within the revised BMS base case analysis.*

The revised base case analysis adopts all aspects of the ERG's preferred base case analysis with the following differences:

- Retention of the responder-based survival modelling approach (with individual choice of parametric distribution for responders/non-responders as requested by the ERG at the clarification stage, and updated based on statistical fit with the updated data);
- The latest pooled analysis, using the updated data from the CheckMate 032 trial, to generate the survival curves for PFS, OS and TTD;
- A treatment stopping rule, based on the assumption that 100% of nivolumab patients will discontinue after two years of treatment, if they haven't discontinued previously.

In addition, BMS would like to respond to two of the amendments made by the ERG to the economic model, which we believe have been incorrectly implemented. These have subsequently been corrected within the BMS revised base case analysis:

- The approach taken by the ERG to apply a weighting to the patient weight across CheckMate 275 and CheckMate 032 assumes a weighting of 50:50 to both trials. This approach is entirely inconsistent with the incorporation of other trial data within the economic model, e.g. efficacy and quality of life data inputs, which have been

weighted across both trials based on trial size. The appropriate average weight across both trials should be 78.69 kg.

- The approach taken by the ERG to incorporate missed doses within the economic model is not considered appropriate. The ERG approach does not incorporate the shape of the distribution of dose delays, which included delays of <7 days but also >14 days. The approach taken by BMS included both left- and right-skewed patients to ensure the approach included the average dose delay across all patients, and we would therefore argue that our original approach is more appropriate.

Full results of the revised BMS base case analysis are provided within the appendix of this response, and demonstrate nivolumab to be cost-effective versus the relevant comparators in this submission. In addition, results are provided for the ERG and Committee-preferred base case analysis, which includes the changes highlighted above, but uses a standard parametric modelling approach in place of the BMS response-based modelling approach. Even under the ERG and Committee-preferred revised base case analysis, nivolumab represents a cost-effective use of NHS resources for patients in this end-of-life indication.

5. Relevance of paclitaxel comparison for UK clinical decision-making

BMS would like to emphasise the feedback from the clinical experts at the Committee meeting for this appraisal, who clearly stated that paclitaxel represents the standard of care in the UK for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.[6] Indeed, paclitaxel was stated to be preferred to docetaxel due to its availability and favourable adverse-effect profile. This was also confirmed as part of the PLUTO trial, the UK-based trial providing evidence for paclitaxel within this appraisal, where the control arm of paclitaxel was chosen specifically on the basis of previously published phase II data and a survey prior to the study that showed paclitaxel to be the most widely used drug in this setting in the UK.[15] The comparison of nivolumab versus paclitaxel therefore represents the most relevant comparison for this appraisal. In this context, BMS would like to highlight to the Committee that the data used for paclitaxel within the economic model is derived from a UK-only, phase III randomised controlled trial, in which paclitaxel was used in accordance with UK clinical practice.[15] The evidence base for paclitaxel that informs the comparison with nivolumab is therefore a robust and highly UK-relevant evidence source to support decision-making within the UK.

6. Further scenarios for validation

As the final part of our response, and to ensure the Committee are provided with a complete set of scenarios upon which to base their decision, BMS have conducted three further scenarios that adopt the same approaches to modelling survival as those explored as part of the ongoing technology appraisal for pembrolizumab and atezolizumab in urothelial

carcinoma.[4, 5] These further scenarios include the adoption of a treatment waning effect, implemented at both 3 and 5 years, in addition to a piecewise modelling approach. Full results from these scenarios are presented within the accompanying appendix. All three scenarios demonstrate that, irrespective of the survival modelling approach taken, nivolumab is cost-effective versus the relevant comparators to this appraisal, with ICERs falling below the £50,000 per QALY gained threshold across all three scenarios. Taken together, BMS hope that the Committee will be satisfied that the range of alternative scenarios presented as part of this response demonstrate the plausibility of nivolumab to be a cost-effective use of NHS resources in this indication.

Conclusion

BMS would like to thank the Committee for considering this additional information in assessing the cost-effectiveness of nivolumab for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy. We would like to highlight that with the additional economic analyses presented within the appendix of this response, nivolumab is shown to be plausibly cost-effective when using the ERG and Committee's preferred assumptions and associated with ICERs well below the cost-effectiveness threshold when using the BMS response-based modelling approach. Therefore, we hope that the Committee will revisit their preliminary decision and in doing so are able to make a positive recommendation regarding nivolumab for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.

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Appendix

Re: Nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995] – company response to Appraisal Consultation Document (ACD)

Contents

1. CheckMate 275: latest database lock

The latest database lock from CheckMate 275 (2nd October 2017) is the third presented to the Committee, following the initial database lock (30th May 2016) and the second database lock (2nd September 2016), which were presented in the initial submission.

All data from the latest database locks of CheckMate 275 and CheckMate 032 are academic in confidence and should remain confidential until Q2 2018.

Table 1: Overview of clinical effectiveness results from CheckMate 275

Tumour response	Nivolumab (n=270) Second database lock: 2nd Sep 2016	Nivolumab (n=270) Latest database lock: 2nd October 2017
ORR, n (%)	54 (20.0) [95% CI 15.4–25.3]	[redacted]
BOR, n (%)		
CR	8 (3.0)	[redacted]
PR	46 (17.0)	[redacted]
SD	60 (22.2)	[redacted]
PD	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]
Median TTR, months (IQR)	1.94 (1.84–2.50)	-
Median DOR, months (95% CI)	10.35 (7.52–NR)	[redacted]

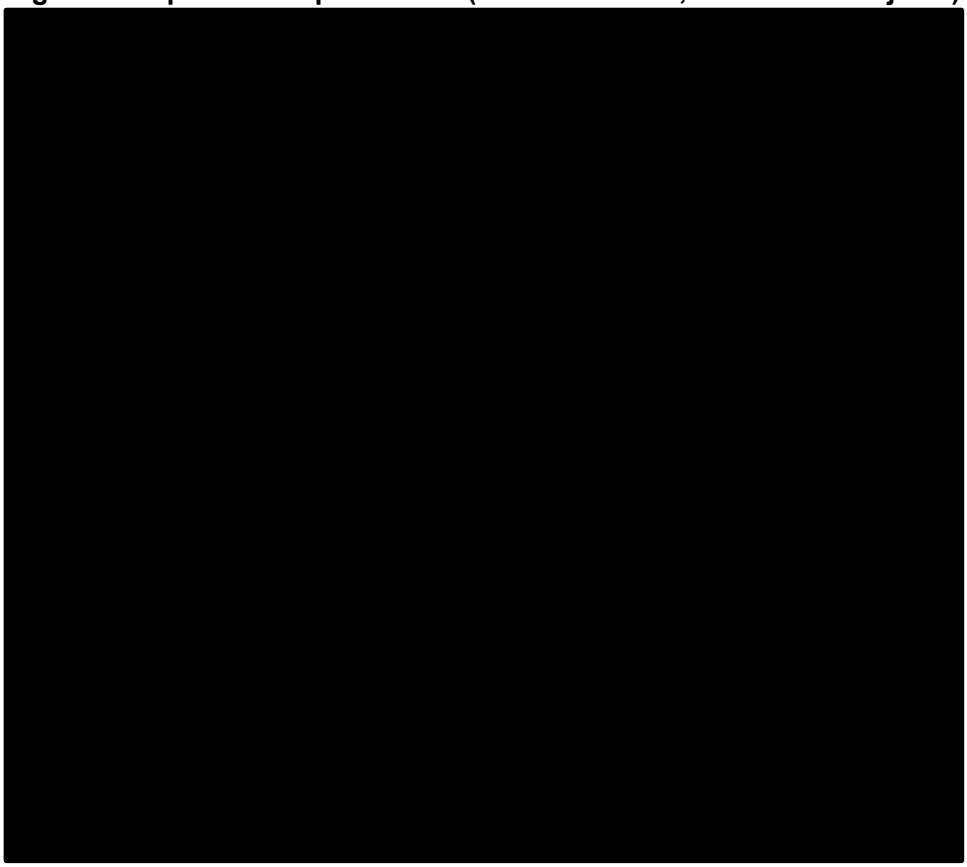
Abbreviations: BOR: best overall response; CI: confidence intervals; CR: complete response; DOR: duration of response; IQR: interquartile range; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease; TTR: time to response NR: not reached.
Source: Bristol-Myers Squibb. CheckMate 275 updated database lock. Data on file.

Median progression-free survival (PFS) was [redacted] and median overall survival (OS) [redacted] from 8.57 months (95% CI: 6.05–11.27). OS rates at 12 months, 18 months, and 24 months from the latest database lock of CheckMate 275 are provided in Table 4. At 24 months, [redacted] were still alive.

Figure 1. Kaplan-Meier Plot for PFS per BIRC (CheckMate 275; all-treated subjects)

Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; PFS: progression-free survival.
Source: Bristol-Myers Squibb. CheckMate 275 updated database lock. Data on file.

Figure 2. Kaplan-Meier plot for OS (CheckMate 275; all-treated subjects)



Abbreviations: CI: confidence interval; OS: overall survival.
Source: Bristol-Myers Squibb. CheckMate 275 updated database lock. Data on file.

Table 2: Overall survival (CheckMate 275; all-treated subjects)

	N at risk	OS rate (95% CI)
Median OS		
Number of events/number patients (%)		
12 months OS		
18 months OS		
24 months OS		

Abbreviations: CI: confidence interval; OS: overall survival.
Source: Bristol-Myers Squibb. CheckMate 275 updated database lock. Data on file.

2. CheckMate 032: latest database lock

An overview of the results from the latest database lock of CheckMate 032 (21st June 2017) alongside the initial database lock results presented within the submission is provided in Table 3.

Table 3: Overview of clinical effectiveness results from CheckMate 032

Tumour response	Nivolumab (n=78) Initial database lock: 24th March 2016	Nivolumab (n=78) Latest database lock: June 21st 2017
ORR, n (%)	19 (24.4) [95% CI 15.3–35.4]	[redacted]
BOR, n (%)		
CR	5 (6.4)	[redacted]
PR	14 (17.9)	[redacted]
SD	22 (28.2)	[redacted]
PD	30 (38.5)	[redacted]
Unable to determine	7 (9.0)	[redacted]
Median TTR, months (IQR)	1.48 (1.25–4.14)	[redacted]
Median DOR, months (95% CI)	NR (9.92–NR)	[redacted]

Abbreviations: BOR: best overall response; CI: confidence intervals; CR: complete response; DOR: duration of response; IQR: interquartile range; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease; TTR: time to response NR: not reached.
Source: Sharma *et* al (2016)[1], CheckMate 032 CSR[2] and Bristol-Myers Squibb CheckMate 032 updated database lock. Data on file.

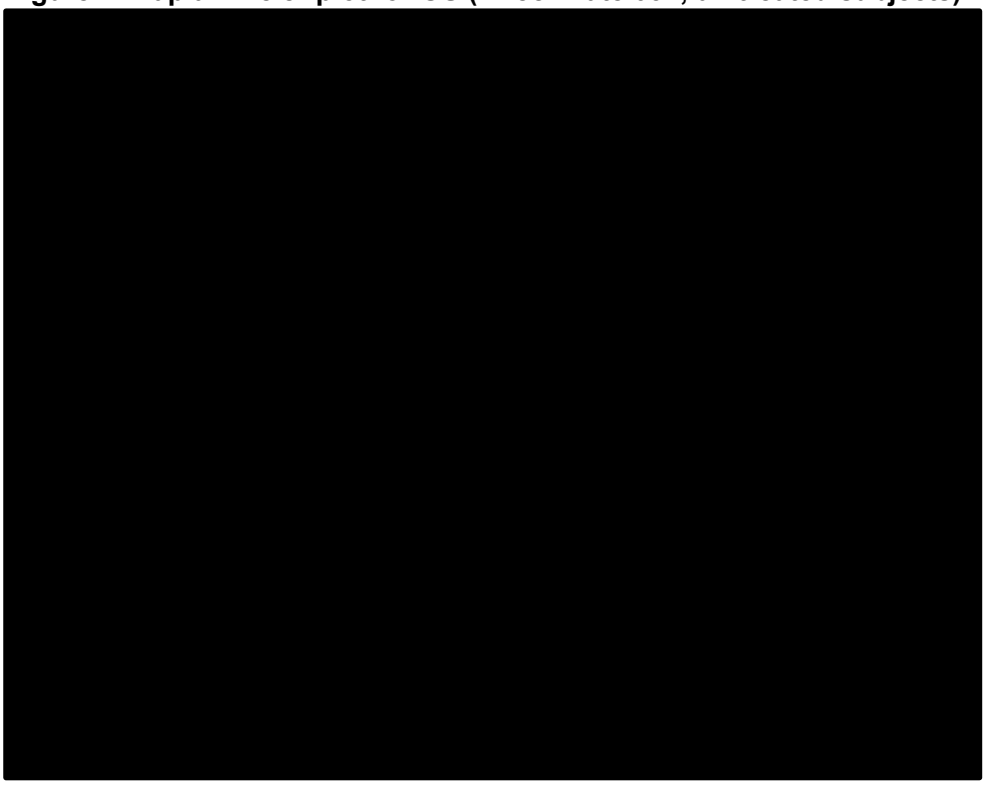
In terms of survival benefits, median PFS was [redacted] from 2.78 months [95% CI: 1.45–5.85] at the previous database lock) and median OS had [redacted] from 9.72 months (95% CI: 7.26–16.16). The Kaplan-Meier plots for PFS and OS from the updated database lock of CheckMate 032 are provided in Figure 3 and Figure 4 below.

OS rates at 12 months, 18 months, and 24 months from the latest database lock of CheckMate 032 are provided in Table 4. At 24 months, [redacted] were still alive

Figure 3: Kaplan-Meier plot for PFS (CheckMate 032; all-treated subjects)

Abbreviations: CI: confidence interval; PFS: progression-free survival.
Source: Bristol-Myers Squibb. CheckMate 032 updated database lock. Data on file.

Figure 4: Kaplan-Meier plot for OS (CheckMate 032; all-treated subjects)



Abbreviations: CI: confidence interval; OS: overall survival.
Source: Bristol-Myers Squibb. CheckMate 032 updated database lock. Data on file.

Table 4: Overall survival (CheckMate 032; all-treated subjects)

	N at risk	OS rate (95% CI)
Median OS		[redacted]
Number of events/number patients (%)		[redacted]
12 months OS	[redacted]	[redacted]
18 months OS	[redacted]	[redacted]
24 months OS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival.
Source: Bristol-Myers Squibb. CheckMate 032 updated database lock. Data on file.

3. Revised BMS base case analysis

Based on the release of the updated results from the latest database lock of CheckMate 032, BMS would like to present to the Committee a revised base case analysis that now includes the more mature data available from CheckMate 032. The revised BMS base case analysis adopts all aspects of the Evidence Review Group (ERG)'s preferred base case analysis with the following differences:

- Retention of the responder-based survival modelling approach (with individual choice of parametric distribution for responders/non-responders as requested by the ERG at the clarification stage, and updated based on statistical fit with the updated data);
- The latest pooled analysis, using the updated data from the CheckMate 032 trial, has been used to generate the survival curves for PFS, OS and TTD;
- A treatment stopping rule, based on the assumption that 100% of nivolumab patients will discontinue after two years of treatment, if they haven't discontinued previously;
- The value for patient weight (kg) has been corrected via the application of a weighted average from the CheckMate 032 and 275 trials. An average value from these two trials was applied in the ERG's model but based on the assumption of equal weight, which is not appropriate given the larger number of patients in the CheckMate 275 trial;
- An average dose delay of all doses is applied, rather than the ERG proposed restriction to doses which are delayed ≥7 days.

In addition to the revised BMS base case analysis, cost-effectiveness results referred to hereafter as the *ERG base case* are also presented, which include the following, important difference:

- The application of standard parametric models, rather than a response-based approach, in line with the preferences of the Committee [ERG base case].

A summary of the selected parametric distributions used for these base case analyses is provided in Table 5 below.

Table 5: Summary of selected distributions for the revised base case

Scenario	Progression-free survival	Overall survival	Time to discontinuation
BMS base case	Response = Generalised gamma No Response = Weibull	Response = Generalised gamma No Response = Log-logistic	Response = Lognormal No Response = Weibull
ERG base case	Generalised gamma	Generalised gamma	Generalised gamma

Both within the revised BMS base case analysis, and the ERG-preferred base case analysis, the incremental cost-effectiveness ratios (ICERs) for paclitaxel, best supportive care (BSC) and the weighted average of paclitaxel/docetaxel combined, are all under the threshold of £50,000 per quality-adjusted life year (QALY) gained.

Table 6: Revised BMS base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)	Paclitaxel/ Docetaxel average (£/QALY)
Nivolumab	[redacted]	3.20	[redacted]					
Paclitaxel	£14,959	1.48	0.97	[redacted]	1.72	[redacted]	£23,497	£25,880
Docetaxel	£13,945	1.73	1.16	[redacted]	1.48	[redacted]	£28,263	
BSC	£9,421	1.20	0.78	[redacted]	2.00	[redacted]	£24,285	

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 7: ERG base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)	Paclitaxel/ Docetaxel average (£/QALY)
Nivolumab	[redacted]	2.12	[redacted]					
Paclitaxel	£14,138	1.02	0.69	[redacted]	1.10	[redacted]	£41,195	£48,045
Docetaxel	£13,358	1.25	0.85	[redacted]	0.88	[redacted]	£54,895	
BSC	£8,970	0.97	0.64	[redacted]	1.15	[redacted]	£45,451	

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Furthermore, a comparison of the QALY gains with nivolumab versus the relevant comparators is provided in Table 10, alongside the QALY gains achieved with pembrolizumab as part of the ongoing technology appraisal in the same indication [ID1019]. As can be seen, within the ERG-

preferred base case for nivolumab, where nivolumab is demonstrated to be cost-effective, the QALY gains for nivolumab are lower than those achieved with pembrolizumab.[3] Therefore, the QALY gains achieved with nivolumab can be considered clinically appropriate based on the modelling assumptions used within our appraisal.

Table 8: Comparison of incremental QALYs gained with pembrolizumab appraisal

Incremental QALYs gained with nivolumab versus comparator				
ID995 (nivolumab)			**ID1019 (pembrolizumab)**	
	Paclitaxel	**Docetaxel**		**Paclitaxel/Docetaxel**
ERG preferred approach	0.71	0.54	**ERG preferred approach**	0.81

Abbreviations: BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

4. Further scenarios for validation

The following further scenarios adopt the same approaches to modelling survival as those explored as part of the ongoing technology appraisals for pembrolizumab and atezolizumab in the same indication and are presented for consistency.[3, 4] These further scenarios include the adoption of a treatment waning effect, implemented at both 3 and 5 years, in addition to a piecewise modelling approach. All three scenarios demonstrate that, irrespective of the survival modelling approach taken, nivolumab is cost-effective versus the relevant comparators to this appraisal, with ICERs falling below the £50,000 per QALY threshold across all three scenarios.

A summary of the selected parametric distributions used for these scenarios is provided in Table 9 below.

Table 9: Summary of selected distributions for the further scenarios for validation

Scenario	Progression-free survival	Overall survival	Time to discontinuation
1) 3-year treatment waning effect	Same distributions as revised BMS base case		
2) 5-year treatment waning effect	Same distributions as revised BMS base case		
3) Piecewise approach	Gompertz (10-week cut-off	Lognormal (40-week cut-off)	Log-logistic (26-week cut-off)

Treatment waning effect scenario

The scenarios presented below include a 3-year and 5-year treatment waning effect (whereby the treatment effect on PFS and OS has ceased at these timepoints (i.e. a hazard ratio of 1), for both the BMS base case analysis (using a response-based modelling approach) and the ERG-preferred base case analysis (using a standard parametric survival modelling approach). All other assumptions remain as outlined above.

Table 10: BMS base case with 3-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	3.20	[redacted]				
Paclitaxel	£15,327	1.66	1.09	[redacted]	1.54	[redacted]	£25,752
Docetaxel	£13,657	1.66	1.10	[redacted]	1.54	[redacted]	£27,643
BSC	£9,223	1.10	0.72	[redacted]	2.10	[redacted]	£23,359

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 11: ERG base case with 3-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	2.12	[redacted]				
Paclitaxel	£14,340	1.13	0.75	[redacted]	1.00	[redacted]	£44,907
Docetaxel	£11,728	1.15	0.76	[redacted]	0.98	[redacted]	£49,468
BSC	£8,659	0.82	0.54	[redacted]	1.30	[redacted]	£40,640

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 12: BMS base case with 5-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	3.20	[redacted]				
Paclitaxel	£15,032	1.52	1.00	[redacted]	1.69	[redacted]	£23,908
Docetaxel	£13,933	1.64	1.09	[redacted]	1.56	[redacted]	£27,220
BSC	£9,267	1.12	0.73	[redacted]	2.08	[redacted]	£23,556

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 13: ERG base case with 5-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	2.12	[redacted]				
Paclitaxel	£14,171	1.04	0.70	[redacted]	1.08	[redacted]	£41,756
Docetaxel	£12,096	1.13	0.75	[redacted]	0.99	[redacted]	£48,780
BSC	£8,702	0.84	0.56	[redacted]	1.28	[redacted]	£41,243

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Piecewise analysis scenario

The following scenarios adopt a piecewise analysis, in line with the approach explored by the ERGs for the technology appraisals of pembrolizumab and atezolizumab in the same indication.[3, 4] Table 14 provides the results of the piecewise analysis only; results from the combination of the piecewise analysis with a 3-year and 5-year treatment waning effect are presented in Table 15 and Table 16, respectively. In both scenarios, the ICERs for nivolumab versus the relevant comparators fall well below the ICER threshold considered by NICE for end-of-life indications, demonstrating nivolumab to remain a cost-effective use of NHS resources in this indication versus current standard of care.

Table 14: BMS base case analysis – piecewise analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	2.55	[redacted]				
Paclitaxel	£14,469	1.20	0.80	[redacted]	1.35	[redacted]	£30,924
Docetaxel	£15,124	1.49	1.03	[redacted]	1.06	[redacted]	£39,634
BSC	£9,218	1.10	0.72	[redacted]	1.46	[redacted]	£33,460

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 15: Piecewise analysis with 3-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)	Paclitaxel/ Docetaxel average (£/QALY
Nivolumab	[redacted]	2.55	[redacted]					
Paclitaxel	£14,777	1.36	0.90	[redacted]	1.20	[redacted]	£34,004	£35,080
Docetaxel	£14,118	1.36	0.93	[redacted]	1.19	[redacted]	£36,156	
BSC	£8,877	0.93	0.61	[redacted]	1.63	[redacted]	£30,666	

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 16: Piecewise analysis with 5-year treatment waning effect

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Nivolumab (£/QALY)	Paclitaxel/ Docetaxel average (£/QALY
Nivolumab	[redacted]	2.55	[redacted]					
Paclitaxel	£14,525	1.23	0.82	[redacted]	1.32	[redacted]	£31,439	£33,573
Docetaxel	£14,070	1.34	0.92	[redacted]	1.21	[redacted]	£35,707	
BSC	£8,923	0.95	0.63	[redacted]	1.60	[redacted]	£31,014	

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

5. Summary of changes made to the ERG economic model

A number of amendments have been made to the model produced by the ERG (the model entitled 'ERG scenarios DEF 30082017KM [ACIC]') to facilitate the additional analyses undertaken for this ACD response. These amendments are summarised in Table 17.

Table 17: Summary of amendments to the economic model

Amendment number	Description	Cells amended in model
1	Mean patient weighted updated to 78.69kg, based on a weighted average of patient weight recorded in CheckMate -032 and -275 trials (weighting necessary due to the different study population sizes).	'Set-Up' sheet – cells E28 and F28
2	Survival curve analysis updated based on the latest pooled data (i.e. original CheckMate -275 data and latest CheckMate -032 data). This required the addition of new survival curve coefficients for PFS, OS and TTD. New coefficients were added for the 8-week and 26-week landmark analysis and also the standard parametric approach (i.e. no landmark).	'PFS & OS' sheet: - Cells BP37:BT49 - Cells BP56:BT68 - Cells BP75:BT87 'Discontinuation sheet: - Cells AB27:AB39 - Cells BR48:BS60 - Cells BR65:BS77
3	Addition of piecewise analysis with the following time frames: - PFS is 10 weeks - OS is 40 weeks or 56 weeks (40 weeks adopted for ACD response) - TTD is 26 weeks	'PFS & OS' sheet: - Additional functionality included to allow piecewise analysis to be selected and to choose between distributions (cells D14:J16). - Additional survival analysis coefficients and formulae for calculations included (cells FQ14:GU470). - Original formulae for survival analysis calculations updated such that the piecewise analysis is adopted to estimate long-term PFS and OS when the piecewise option is selected (cells DL21:DM470). 'Discontinuation' sheet: - Additional functionality included to allow piecewise analysis to be selected and to choose between distributions (cells L11:N12). - Additional survival analysis coefficients and formulae for calculations included (cells CS16:DE471). - Original formulae for survival analysis calculations updated such that the piecewise analysis is adopted to estimate long-term TTD when the piecewise option is selected (cells AH27:AH447).

4	The Cholesky decomposition matrices for PFS and OS have been updated so the probabilistic sensitivity analysis runs with the latest pooled data.	'Chol Decomp – PFS' sheet: All of the covariance matrices have been updated (cells B25:AZ40 [Weibull, Gompertz, Lognormal and Log-logistic], M5:S9 [exponential], BD28:BM46 [Generalised gamma]). 'Chol Decomp – OS' sheet: All of the covariance matrices have been updated (cells B25:AZ40 [Weibull, Gompertz, Lognormal and Log-logistic], M5:S9 [exponential], BD28:BM46 [Generalised gamma]).

References

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2. Bristol-Myers Squibb. CheckMate 032: Clinical Study Report for Study CA209032 (29th June 2016).
3. National Institute for Health and Care Excellence (NICE). [ID1019]: Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma. Available: https://www.nice.org.uk/guidance/indevelopment/gid-ta10113 [Accessed 30 Oct 2017].
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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating metastatic or unresectable urothelial cancer: critique of BMS submission of November 9th 2017

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Date completed	30/08/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 16/108/11.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Armstrong N, Grimm S, Ramaekers BLT, Pouwels X, Lang S, Fayter D, Petersohn S, Riemsma R, Worthy G, Stirk S, Ross J, Joore MA, Kleijnen J. Nivolumab for treating metastatic or unresectable urothelial cancer: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2017.

Contributions of authors

Nigel Armstrong acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels and Svenja Petersohn acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Shona Lang and Rob Riemsma acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk and Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

Ab	Antibody
AE	Adverse Events
AIC	Akaike information criterion
ALT	Alanine transaminase
BI	Budget impact
BIC	Bayesian information criterion
BIRC	Blinded independent review committee
BNF	British National Formulary
BOR	best overall response
BSA	body surface area
BSC	Best supportive care
CDF	Cancer Drugs Fund
CD28	Cluster of differentiation 28
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Carcinoma in situ
Cis	Cisplatin
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CHMP	Committee for Medicinal Products for Human Use
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events (NCI)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
"D" ¯ "res"	Residual deviance
DIC ¯	Deviance information criteria
DOR	Duration of response
DSU	Decision Support Unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FP	Fractional polynomial
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
Gem	Gemcitabine
GFR	Glomerular filtration rate
GP	General practitioner

HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
IFNγR	Interferon gamma receptor
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LPFT	Last patient first treatment
LYG	Life years gained
LYS	Life Year Saved
LYs	Life years
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
MICE	Multiple imputation by chained equations
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NA	Not applicable
NCI	National Cancer Institute
NF-κB	Nuclear transcription factor-κB
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not Reached/Not Reported
NSCLC	Non-small cell lung cancer
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
pD	Number of effective parameters
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PH	Proportional hazards
PP	Post-progression
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PROs	Patient-reported outcomes
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU HCHS	Personal and Social Services Research Unit Hospital and Community Health Services

PI3K	Phosphoinositide 3-kinase
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Events
SD	Stable disease/Standard deviation
SE	Standard error
Shp-2	Src homology 2 domain-containing protein tyrosine phosphatase 2
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TNM	Tumour-node-metastasis
TTD	Time to treatment discontinuation
TTR	Time to response
TURBT	Transurethral resection of the bladder tumour
UC	Urothelial carcinoma
UICC	Union for International Cancer Control
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
WHO	World Health Organisation

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1. Approach to modelling long-term survival

The company claim in their response to the ACD that the basis for the Committee's decision relies on the adoption of standard parametric survival analysis in lieu of a response-based modelling approach.[1] They state that it has been criticised by previous NICE Committees, citing the appraisal of nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971].[2] The appraisal of pembrolizumab is also cited to support a piecewise vs. fully parametric approach.[3] They also state that it is not supported by the clinical evidence available and that it does not characterise the survival benefit that can be achieved with immunotherapies such as nivolumab.

The ERG would like to point out that, whilst there has been criticism of the fully parametric approach to survival modelling, this does not imply that it might not be a legitimate method to consider in the context of uncertainty as to which of many methods is most accurate. It is also important to note that the response-based method chosen by the company for this appraisal is only one alternative to a fully parametric method, which also includes piecewise parametric models. Moreover, it has not been recommended in the ACD of any appraisal to the knowledge of the ERG. In particular, the method preferred in the ACD of nivolumab for SCCHN was a piecewise model using the Kaplan-Meier curve for the first part of the time horizon, after which a parametric model was fitted.[2] As discussed in the original ERG report, the ERG prefers a standard parametric approach given that:

- the response-based approach is not supported by data,
- the company did not justify:
    - why the standard approach is inappropriate in this specific case and
    - why the 'landmark approach', necessitating additional assumptions (e.g. selection of the 8-week landmark point) is superior (see section 5.2.6 of the ERG report for more detailed argumentation).[4]

2. Updated survival data from CheckMate 275 and CheckMate 032

The company have provided updated survival data for CheckMate 275 and CheckMate 032 with results shown in the Appendix.[5]

These show, in comparison to the values in the original CS, [redacted] for CheckMate 032 and [redacted] for CheckMate 275.[5, 6] The Appendix also states that, at 24 months, [redacted] were still alive in CheckMate 275 and CheckMate 032 respectively.

Based on these data and given that CheckMate 032 is the smaller study the ERG would conclude that the latest data essentially confirm their findings based on the original CS.[4] As such, given that these remain data for only nivolumab and not comparative data, as concluded in the original ERG report, it is difficult to be sure what the effectiveness of nivolumab is in comparison to the comparators in the scope. Evidence from directly examining the single arms of the trial data indicates little difference between the outcomes measured from the nivolumab and comparator studies. Such a naive comparison carries a high risk of bias. STC analysis was used to try and reduce this bias, but there is also no clear evidence that risk of bias was reduced by the STC analysis. Multiple limitations in the STC were identified and the test of validity recommended by TSD 18, the 'out-of-sample' method lacked success in reducing the bias (if it is applicable at all given the lack of data and FP model). The ERG was able to estimate the unadjusted hazards for nivolumab, but not with estimates of uncertainty. The effect of an analysis based on different combinations of covariates in the prediction model used to make the adjustment remains unknown.

Table 1: Overview of clinical effectiveness results from CheckMate 275 and CheckMate 032

Outcome	CheckMate 275			CheckMate 032	
	Initial database lock: 30 May 2016 n=265[c]	Latest database lock: 2 Sep 2016 n=270[c]	Latest database lock: 2nd October 2017 n=270*	Initial database lock: 24th March 2016 n=78	Latest database lock: June 21st 2017 n=78*
ORR, n (%), [95% CI]	52 (19.6), [15.0–24.9]	54 (20.0), [15.4–25.3][b]	[redacted]	19 (24.4) [15.3–35.4]	[redacted]
TTR, median (IQR), months	1.87 (1.81–1.97)[a]	1.94 (1.84–2.50)[b]	-	1.48 (1.25–4.14)	[redacted]
DOR, median (95% CI), months	NR (7.43–NR)[a]	10.35 (7.52–NR)[b]	[redacted]	NR (9.92–NR)	[redacted]
PFS, median (95% CI), months	2.00 (1.87–2.63)[a]	2.00 (1.87–2.63)[b]	[redacted]	2.78 (1.45–5.85)	[redacted]
OS, median (95% CI), months	8.74 (6.05–NR)[a]	8.57 (6.05–11.27)[b]	[redacted]	9.72 (7.26–16.16)	[redacted]

Source: CS, Table 11, page 43 except *BMS ACD response appendix

[a]Minimum follow-up of 6 months from the date of first dose. [b]Minimum follow-up of 8.3 months. [C]Follow-up for the latest database lock was sufficient to include 5 patients from Japan who were not included in efficacy analyses in the initial database lock. CI = confidence intervals; DOR = duration of response; NR = not reached.ORR = objective response rate; OS = overall survival; PFS =progression free survival; TTR = time to response

3. Application of a two-year treatment stopping rule

The company argues that:

> *"The application of a two-year treatment stopping rule (at which point 100% of patients cease treatment) has been mandated by NHS England as part of the positive recommendations by NICE in the most recent appraisals for nivolumab as a treatment for metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811], previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900] and recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]."*

It should however be noted that the application of a two-year treatment stopping rule is not as undisputed as it might appear based on the above-mentioned statement from the company. For instance, in ID971, the committee's preferred assumption for the most plausible ICER was without a stopping rule. Also, the committee concluded that:

> *"it would not consider a stopping rule for routine commissioning" … "it would only consider analyses with the stopping rule in the context of potential inclusion in the cancer drugs fund, as an approach to managing risk".*

As for ID971, nivolumab is recommended for use within the Cancer Drugs Fund in both ID811 and ID900.

Additionally, the company attempts to provide a clinical rationale for the stopping rule by stating, based on the CheckMate 003 trial, that:

> *"ongoing responses after treatment cessation were observed in this trial for both patients with advanced NSCLC and melanoma who had completed 96 weeks of therapy with nivolumab"*

It is unclear to the ERG why this argument would justify a 2-year stopping rule in the current population. Moreover, implementing a stopping rule focusing on treatment discontinuation only, in the model would reduce the treatment costs while maintaining the effectiveness of continued treatment. Although it might be biologically plausible for treatment effects to continue after stopping treatment, the exact continued effect is uncertain.

4. Revised BMS base-case analysis

The company provided a revised base-case using updated data from CheckMate 032.[1] However, it should be noted that due to time constraints the updated data from CheckMate 275 have not been incorporated in this revised base-case analysis. The ERG considers this to be a serious limitation, which might be labelled as cherry-picking, given that the median survival in CheckMate 032 is higher than in CheckMate 275 (See Table 1). It should further be noted that CheckMate 275 is a much larger study, and the company did not provide detail on the pooling method of both studies. This means that it is unclear whether data from both studies were appropriately incorporated in the model. Hence the updated results should be interpreted with this in mind.

In its revised base-case the company adopts all aspects of the ERG's preferred base-case analysis with the following differences:

1. Retention of the responder-based survival modelling approach

2. The latest pooled analysis, using the updated data from the CheckMate 032 trial to generate the survival curves for PFS, OS and TTD;
3. A treatment stopping rule, based on the assumption that 100% of nivolumab patients will discontinue after two years of treatment, if they have not discontinued previously.

Additionally, the company changed two amendments made by the ERG to the economic model:

4. The approach taken by the ERG to apply a weighting to the patient weight across CheckMate 275 and CheckMate 032. The company prefers to calculate a weighted mean instead of an unweighted mean to calculate patient weight.
5. The approach taken by the ERG to incorporate missed doses within the economic model.

The ERG agrees with the use of updated data from the CheckMate 032 trial (item 2), but highlights the abovementioned inconsistency that updated data from CheckMate 275 were not included. The use of a weighted mean instead of an unweighted mean to calculate patient weight (item 4) is considered reasonable by the ERG (resulting in a weight of 78.69 kg).

The ERG disagrees with the other deviations (items 1, 3 and 5). The response-based approach (item 1) is not supported by data and the company did not justify why the standard approach is inappropriate in this specific case and why the 'landmark approach', necessitating additional assumptions (e.g. selection of the 8-week landmark point) is superior (see section 5.2.6 of the ERG report for more detailed argumentation).[2] The ERG critique on the treatment stopping rule (item 3) is presented in section 3 of this document. Finally, it is unclear why the company believes the approach taken by the ERG to incorporate missed doses within the economic model (item 5) is wrong. Hence, the ERG prefers to incorporate this adjustment, assuming a missed dose only in case the length of a delay exceeded seven days. This resulted in a dose intensity of 95.8% (see section 5.2.9 of the ERG report for more detailed argumentation).[2]

The ERG noticed that the company changed the parametric distributions used for estimating overall survival (OS), progression free survival (PFS) and time to treatment discontinuation (TTD). This includes different distributions for responders and non-responders which was not considered in the original company submission. See Table 5 in the Appendix of the company response to the ACD for more details.[5] Given the lack of justification for this change, the ERG prefers to maintain its preferences to use the generalised gamma distribution for OS, PFS and TTD. However, based on informal exploratory analyses, the ERG noted that the company's change in choice of parametric curves did not cause substantial changes to the ICERs.

Finally, the ERG noted that the company attempted to replicate the original ERG base-case with the new data in their ACD response.[1] The ERG was unable to reproduce the company's estimates of the ERG base-case, and therefore suggests to interpret these with caution.

The revised company and ERG base-case are presented in Tables 2 and 3 respectively. The ERG's changes to the company's base-case include: the use of the conventional, fully parametric, approach to estimating survival, not using the stopping rule, and the calculation of missed doses as per the original ERG base-case. The ERG maintained the company's update to effectiveness data and the company's change to deriving patient weight. It should be noted that the marked change in ICERs in the revised ERG base-case compared with the original ERG base-case is produced entirely by the CheckMate 032 data update (and to a minimal extend by the weighting by using a weighted average to calculate patient weight), provided that no further changes were made to the model by the company.

Table 2: Company's revised base-case results (deterministic); Gem+Cis added by ERG

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£13,945	1.16	[redacted]	[redacted]	£28,263
Paclitaxel	£14,959	0.97	[redacted]	[redacted]	£23,497
Gem+Cis	£32,135	1.87	[redacted]	[redacted]	£38,338
BSC	£9,421	0.78	[redacted]	[redacted]	£24,285

Table 3: ERG revised base-case results (deterministic, nivolumab with PAS)

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER versus Nivolumab (£/QALY)**
Nivolumab	[redacted]	[redacted]			
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£78,869
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£58,791
Gem+Cis	£30,205	1.44	[redacted]	[redacted]	Nivolumab is dominated
BSC	£8,995	0.65	[redacted]	[redacted]	£62,352

5. Relevance of paclitaxel comparison for UK decision-making

BMS cited the feedback from the clinical experts at the Committee meeting for the appraisal, who they say clearly stated that paclitaxel represents the standard of care in the UK for patients with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy.[7] They also cite the choice of paclitaxel as comparator in the PLUTO trial.[8]

However, the ERG would like to point out that there is an expectation that comparison is made with all comparators in the scope and not only one chosen by whichever criteria are selected, whether those be frequency of use or clinical opinion. Indeed, although the ACD records that the clinical experts stated that paclitaxel is used as current standard of care in the UK because of its availability and favourable

adverse-effect profile compared with docetaxel, the committee concluded that docetaxel, paclitaxel, and best supportive care are appropriate comparators.[7]

6. Further scenarios for validation

In addition to its base-case, the company also provided a range of scenario analyses.[1] This included scenarios incorporating treatment waning and a piecewise approach. The company argued that their ICERs fall below the £50,000 per QALY gained threshold and hence this demonstrates the plausibility of nivolumab to be a cost-effective use of NHS resources. This is however not convincing to the ERG given the issues highlighted in section 4 of this document (in particular that the updated data from CheckMate 275 were not included and the lack of justification for the changed parametric survival distributions) and given that this statement is not applicable to the revised ERG base-case. In the revised ERG base-case the ICERs range from £58,791 per QALY gained to nivolumab being dominated.

The ERG explored the 2-year treatment stopping rule in exploratory analysis, conditional on the revised ERG base-case (Table 4).

Table 4. ERG scenario with 2-year treatment stopping rule (deterministic, nivolumab with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus Nivolumab (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£13,619	0.86	[redacted]	[redacted]	£57,253
Paclitaxel	£14,124	0.69	[redacted]	[redacted]	£42,480
Gem+Cis	£30,205	1.44	[redacted]	[redacted]	Nivolumab is dominated
BSC	£8,995	0.65	[redacted]	[redacted]	£46,968

7. Conclusion

There remains substantial uncertainty about the ICERs generated by the company and the ERG. Uncertainties discussed in the ERG report, for example, the use of single arm studies to derive effectiveness and the method for the pooling of CheckMate 275 and 032 studies, remain unresolved.[4] More uncertainty was introduced by lack of clarity surrounding the use of data updates in the model, in particular the omission of the CheckMate 275 update. Furthermore, it should be noted that exploratory analyses in the original ERG report in an attempt at quantifying the impact of alternative assumptions had mostly an upward effect on the ICERs. In conclusion, given the revised ERG base-case ICERs are estimated to be above £50,000 per QALY gained, and the large uncertainty regarding (comparative) treatment effectiveness in combination with the lack of appropriate validation, uncertainty around the cost effectiveness of nivolumab remains substantial.

8. References

[1] Bristol-Myers Squibb. *Nivolumab for treating adults with locally advanced unresectable or metastatic urothelial carcinoma after failure of platinum-based chemotherapy [ID995] – company response to Appraisal Consultation Document (ACD)*. Middlesex: Bristol-Myers Squibb, 2017. 10p.

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