NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID1182]

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
   - Kidney Cancer Support Network
   - Royal College of Physicians on behalf of the NCRI-ACP-RCP-RCR

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

4. **Appendix of new evidence –** submitted by Bristol-Myers Squibb

5. **Evidence Review Group critique of company response** – prepared by the Liverpool Reviews and Implementation Group (LRIG)

6. **Bristol-Myers Squibb proposal for recommendation for use in the Cancer Drugs Fund (CDF)**

7. **Evidence Review Group critique of the Cancer Drugs Fund proposal**

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

Nivolumab with ipilimumab for untreated advanced renal cell carcinoma

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 Social Care 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 document (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 and Social Care, 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	Consultee (company)	BMS	**30-month DBL CheckMate 214 data** **Clinical effectiveness data** Figure 1 shows CheckMate 214 30-month DBL OS data in the form of Kaplan–Meier (KM) curves, alongside the CS-preferred and committee-preferred OS extrapolations, based on 18-month DBL data. Also shown in Figure 1: time to subsequent therapy of death KM curves based on the 30-month DBL, as presented at ESMO 2018.[1] **Figure 1: Extrapolation of CheckMate 214 OS data using the 7 August 2017 database lock compared to KM plots from 6 August 2018 and time to subsequent therapy or death from McDermott et al.[1]***	Comment noted. The additional data cut provided by the company was considered by the Appraisal Committee at the second meeting. Figures noted.

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
			 **Key:** KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival. **Notes:** Time to subsequent therapy or death KM data were digitised from McDermott et al. Other KM data are based on patient-level data from the CheckMate 214 August 2018 database lock. * zero IO survival effect assumed for “Committee” curves, which is not in line with committee preferences, as stated in ACD Section 3.17. Figure 1 highlights two key implications of the 30-month DBL OS data. First, OS extrapolations for NIVO+IPI patients based on the 18-month DBL under-predict observed survival in the 30-month DBL. This is true for both the company-preferred (log-normal) and committee-preferred (KM + exponential) survival models. Second, OS extrapolations for sunitinib patients based on the 18-month DBL under-predict observed survival in the 30-month DBL. Again, this is true for both the company-preferred (log-normal) and	

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			committee-preferred (KM + exponential) survival models, to a greater extent than for the NIVO+IPI patients. This is explained by the November 2017 trial protocol amendment, after the primary endpoint of the trial had been met, allowing patients on the sunitinib arm to crossover to the NIVO+IPI arm,[5] and illustrated by the time to subsequent therapy or death KM curves in Figure 1. Although approximately [redacted] of patients on the sunitinib arm are alive at 44 months, only [redacted] of patients on the sunitinib arm are alive and not on subsequent therapy. Nivolumab monotherapy was the most commonly received subsequent therapy on the sunitinib arm of CheckMate 214, with [redacted] of the [redacted] patients receiving subsequent therapy ([redacted]) receiving subsequent nivolumab as of the 18-month DBL. It is therefore likely that the majority of patients alive on the sunitinib arm at the latest data cut-off will have received NIVO+IPI or nivolumab monotherapy as a subsequent therapy. We performed survival analyses on 30-month DBL OS data and incorporated this into the economic model in order to provide the functionality to meet committee preferences, as per the economic model submitted alongside the "ID1182 Company additional evidence submission" document.[2] We were also able to do this for time-to-discontinuation (TTD) data and show committee-preferred (KM + exponential) model fits to these data in Figure 2. Alongside these curves in Figure 2 are the committee-preferred TTD models based on 18-month DBL data, the 30-month DBL OS KM data and committee-preferred (KM + exponential) extrapolations of these data and the 18-month DBL OS data. The Aug-18 curves in Figure 2 represent the updated OS and TTD data informing updated committee-preferred cost-effectiveness results, presented in Part **Error! Reference source not found.**, with one caveat, also noted below Figure 1. In Section 3.17 of the ACD, the committee note, in divergence from the ERG's preferences for analysis, that it may be reasonable to include an immunological effect. We attempt to explicitly capture the committee's preferences on this point in Part **Error! Reference source not found.**, but here note that Figure 2 extrapolations do not include an immunologic effect. Instead, overall survival extrapolations including a range of immunologic effect probabilities using the committee preferences are shown in Figure 3. Section 3.17 of the ACD also notes the committee's preference for independent radiology review committee (IRRC)-assessed progression free survival (PFS) data, in contrast to the ERG's preference on this point. [redacted] However, as the committee note in Section 3.18 of the ACD, cost-effectiveness results are less sensitive to PFS uncertainty than TTD and OS uncertainty. For this reason and for clarity, we have restricted the data presented in Figure 2 to TTD and OS data. **Figure 2: 30-month DBL OS and TTD KM data, extrapolated using committee-preferred assumptions***	

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			 **Key:** KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; TTD, time to discontinuation. * zero IO survival effect assumed in Figure 2, which is not in line with committee preferences, as stated in ACD Section 3.17. **Figure 3: 30-month DBL OS KM data, extrapolated using committee-preferred assumptions and varying probabilities of immunologic effect occurring** **Key:** IO prob, probability of immunologic effect occurring; KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.	
2	Consultee (company)	BMS	**Health-related quality of life data** Section 3.14 of the ACD states the preference for disease progression to be included as a variable in	Comment noted. The committee

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 base case utility analysis. We have updated the analysis to align with the committee's preference. In our original analysis, we used the model without this variable in the CS on the basis of statistical goodness-of-fit, through the stepwise selection process described in Section B.3.4.1 of the CS. We have updated our analysis of CheckMate 214 patient-reported EQ-5D-3L data using EQ-5D-3L data from the 30-month DBL. Table 1 shows parameter values and model fits from the stepwise variable selection process using the 30-month DBL data, and is analogous to Table 28 of CS Section B.3.4.1. The best fitting model in Table 1; Model 7; aligns with the committee's stated preferences for analyses of these data. Table 2 shows the mean health state utility values implied by Model 7 of Table 1, alongside the mean health state utility values from the CS base case, for comparison. When interpreting these data, as for 30-month OS data, it is important to consider the likely impact of treatment crossover and subsequent nivolumab monotherapy for sunitinib arm patients in "off treatment" health states. **Table 1: Results from stepwise variable selection approach to mixed model analysis of CheckMate 214 intermediate-/poor-risk EQ-5D-3L utility data (6 August 2018 DBL)**	considered the additional health related quality of life data and agreed that progression status should be included in the model, however, it noted that the cost-effectiveness estimates were unlikely to be sensitive to the utility values used in the model. (Final Appraisal Determination Section 3.16)

	Estimate (SE), P-Value						
Parameters/Fit Statistics	**Model 1: intercept only**	**Model 2: add Treatment Arm**	**Model 3: add Progression Status**	**Model 4: add Treatment Status**	**Model 5: add Treatment Arm to Model 4**	**Model 6: add Progression Status to Model 4**	**Model 7: add Progression Status and interactions to Model 5**
Intercept	0.7616 (0.0068), <.0001	0.7790 (0.0096), <.0001	0.7671 (0.0069), <.0001	0.7740 (0.0069), <.0001	0.7938 (0.0097), <.0001	0.7734 (0.0069), <.0001	0.7933 (0.0097), <.0001
Treatment Arm (Sunitinib)		-0.0351 (0.0136), 0.0102			-0.0397 (0.0138), 0.0040		-0.0398 (0.0138), 0.0040
Progression Status (Progression)			-0.0343 (0.0052), <.0001			0.0052 (0.0072), 0.4700	0.0006 (0.0093), 0.9451
Treatment Status (Off treatment)				-0.0568 (0.0045), <.0001	-0.0679 (0.0066), <.0001	-0.0454 (0.0061), <.0001	-0.0441 (0.0092), <.0001
Treatment Arm*Progression Status							0.0092 (0.0146), 0.5289
Treatment Arm*Treatment Status					0.0208 (0.0091), 0.0220		-0.0024 (0.0124), 0.8462
Progression Status*Treatment Status						-0.0284 (0.0107), 0.0082	-0.0480 (0.0150), 0.0014
Treatment Arm*Progression Status*Treatment Status							0.0383 (0.0217), 0.0770
-2 Log Likelihood	-7441.7	-7448.2	-7484.4	-7597.9	-7609.7	-7605.8	-7624.3
AIC (smaller is better)	-7435.7	-7440.2	-7476.4	-7589.9	-7597.7	-7593.8	-7604.3
AICc (smaller is better)	-7435.7	-7440.2	-7476.4	-7589.8	-7597.7	-7593.8	-7604.3
BIC (smaller is better)	-7421.5	-7421.3	-7457.5	-7570.9	-7569.3	-7565.4	-7557

Key: AIC; Akaike information criterion; AICc, Akaike information criterion with a correction for small samples; BIC; Bayesian information criterion; SE, standard error.

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<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 2: Comparison of utility values from regression analysis of the August 2017 and August 2018 DBLs

<table>
<tr><th>Database lock</th><th colspan="2">NIVO+IPI</th><th colspan="2">Sunitinib</th></tr>
<tr><th></th><th>Aug-17</th><th>Aug-18</th><th>Aug-17</th><th>Aug-18</th></tr>
<tr><td>PFS on treatment utility</td><td>0.793</td><td>0.793</td><td>0.751</td><td>0.754</td></tr>
<tr><td>PFS off treatment utility</td><td>0.719</td><td>0.749</td><td>0.699</td><td>0.707</td></tr>
<tr><td>PPS on treatment utility</td><td>0.793</td><td>0.794</td><td>0.751</td><td>0.763</td></tr>
<tr><td>PPS off treatment utility</td><td>0.719</td><td>0.702</td><td>0.699</td><td>0.707</td></tr>
<tr><td colspan="5">Key: PFS, progression-free survival; PPS, post-progression survival</td></tr>
</table>

</td><td></td></tr>
<tr><td>3</td><td>Consultee (company)</td><td>BMS</td><td>

<table>
<tr><th>Assumption category</th><th>Stated or interpreted Committee preference</th><th>January 2019 Company preference</th></tr>
<tr><td>Immunological effect</td><td>25% probability of immunological survival effect for durable responders only.
<u>Justification</u>
ACD 3.10: “The committee concluded that the size of any immunological effect is highly uncertain and could lie somewhere between the company’s optimistic [50%] and ERG’s conservative assumptions [0%]”</td><td>50% probability of immunological survival effect for durable responders only.
<u>Justification</u>
We recognise the high level of uncertainty here and in the CS. We have attempted to base our assumptions on as much evidence as possible. Clinical opinion was that this effect would only occur in those patients who have a durable response, and that these patients would be likely to experience a long-term survival benefit.[6] The proportion of patients from CheckMate 214 (CheckMate 025 for second-line nivolumab) who were experiencing a durable response was used to inform the proportion who could potentially experience a long-term immunological effect (as per the NICE technology</td></tr>
</table>

</td><td>Comment noted. The Appraisal Committee concluded that there was no robust evidence on the size of the association between a clinically meaningful definition of response and long-term survival with nivolumab and ipilimumab. The committee considered that the Cancer Drugs Fund could be used to resolve clinical uncertainty surrounding this issue. (Section 3.10 and 3.26 of the Final Appraisal Determination)</td></tr>
</table>

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					appraisal for nivolumab monotherapy in previously treated RCC patients [TA417][7]). A model input for the probability of this effect was incorporated as an uncertain parameter; specifically, a 50% probability of an immunological survival effect being borne out is assumed. The probability of an IO effect remains unknown, but given clinical expectations and data available now, we do not believe our assumptions are implausible, or even necessarily optimistic. If such an effect is likely for durable responders, our approach is conservative.	
4	Consultee (company)	BMS	Stopping rule	No stopping rule included. Justification ACD 3.11: "*it is not appropriate to include a stopping rule for decision-making*"	Patients are unlikely to receive nivolumab beyond 2 years and definitely not beyond 5 years. Justification We are open to the use of a stopping rule as part of the recommendation for NIVO+IPI use in untreated RCC. Confidence in a stopping rule and prolonged benefit of NIVO+IPI is demonstrated in [redacted] Scenario analysis using varying probabilities of IO effect, 2- and 5-year treatment stopping rules and treatment waning effects for the company and committee base case analyses were presented in Tables 1-4 of the December 2018 "ID1182 Company additional evidence submission" document.[2] Treatment waning effects were incorporated in this analysis, in a similar manner to those used in the NICE technology appraisals for nivolumab in	Comment noted. The Appraisal Committee considered a stopping rule inappropriate because its effect on clinical outcomes were untested (Final Appraisal Determination Section 3.12)

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					previously treated squamous and non-squamous non-small-cell lung cancer.[8, 9] A treatment stopping rule is appropriate because patients will not receive any additional benefit from remaining on treatment, as the treatment has already worked, and the mechanism of action allows this benefit to continue, whether or not the patient remains on treatment. If this were not the case, treatment waning would occur if a patient discontinued treatment, making a stopping rule ethically problematic. Further, in their submission for this appraisal, NHS England note that "the majority of recent NICE recommendations have included 2 year stopping rules for anti-PD-1 and anti-PD-L1 drugs … there is therefore a clear trend in terms of NICE decision making but its acceptance by clinicians also reflects increasing clinical concern as to the longer term toxicities of such immunotherapy".[10] As such, we believe either a 2 or 5-year stopping rule would not affect the life year or QALYs gain expected for NIVO+IPI.	
5	Consultee (company)	BMS	Time to discontinuation	30-month DBL data used. Justification Data availability; see Part 1.1. Assumed equivalence between sunitinib and pazopanib. Justification ACD 3.13: "*pazopanib and sunitinib are considered clinically equivalent….and time to stopping treatment for pazopanib and sunitinib*	30-month DBL data used. Justification Data availability; Part 1.1. Assumed equivalence between sunitinib and pazopanib. Justification Alignment with ACD 3.13 [redacted] Justification	Comment noted. The additional data cut provided by the company was considered by the Appraisal Committee at the second meeting. (Final Appraisal Determination Section 3.18)

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				should also be considered to be the same" KM followed by exponential curve to extrapolate the data. <u>Justification</u> ACD 3.16: "*The ERG considered that a piecewise model, where Kaplan–Meier data .. are followed by a parametric curve, was appropriate because the proportional hazards assumption was not met and in all the cumulative hazard plots, the curves were parallel at the start then separate. The ERG appended exponential curves to the Kaplan–Meier data because later portions of the cumulative hazard plots showed an exponential trend. The ERG chose 21 to 22 months to switch from Kaplan–Meier data to an exponential curve because after this time point there are few patients remaining, which makes the Kaplan–Meier data uncertain. The ERG note that the extrapolation is not sensitive to the time point chosen for the switch, because the shape of the exponential curve is defined by plotting a straight line on the cumulative hazard plot. The committee agreed that the cumulative hazard plots suggested that using the Kaplan–Meier, followed by an exponential curve, was appropriate to extrapolate the data*."	As per CS, Section B.3.3. While we respect the committee's preferences, we question the appropriateness of using KM data followed by an exponential curve for extrapolation of survival outcomes, given NIVO+IPI's mechanism of action. RCC patients on nivolumab and sunitinib have been shown to have decreasing OS HRs over time, as commented by the ERG in Section 5.4.3 and Figure 8-10 of the ERG report, "[it is] *to be expected, as less fit patients will likely to die earlier than fitter patients and the patients left at risk will have lower mortality risk*". This is arguably truer for immuno-oncology therapies, which are expected to provide a great long-term survival benefit for those who respond to treatment. The cumulative OS hazard from the sunitinib global expanded access trial, the source with greatest number of patients and longest follow-up, shows a continual decrease in hazards, with a linear trend only observed after 30 months. The ERG and thus committee approach is to use a long-term exponential extrapolation for survival, based on the shape of the clinical trial log-cumulate hazards in the last few months of the 18-month data. Scant clinical rational or statistical analysis were used to select the point at which the exponential curve was applied.	

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6	Consultee (company)	BMS	Progression-free survival	Secondary-definition IRRC-assessed PFS data Justification ACD 3.12: "*The committee noted investigator-assessed progression-free survival was not a primary outcome of CheckMate 214 and, being unblinded, it may introduce bias. The committee recalled that it considered progression-free survival results should include people who have subsequent treatment before progression ... The committee concluded that the IRRC-assessed progression-free survival results which included people who have subsequent treatment before progression should be used in the economic model.*" KM followed by exponential curve to extrapolate the data. Justification ACD 3.16: see #3	Secondary-definition IRRC-assessed PFS data Justification Alignment with ACD 3.12. Independent cubic spline 2-knots hazard models fitted to respective NIVO+IPI and sunitinib datasets Justification Combination of best statistical fit and prior clinical input, after re-running survival analyses with the 30-month DBL. See #3 for explanation of why we prefer not to align with committee and ERG preferences for model selection.	Comment noted. The additional data cut provided by the company was considered by the Appraisal Committee at the second meeting. (Final Appraisal Determination Section 3.18)
7	Consultee (company)	BMS	Overall survival	30-month DBL data used. Justification Data availability; see Part 1.1. KM followed by exponential curve to extrapolate the data. Justification ACD 3.16: see #3	30-month DBL data used. Justification Data availability; see Part 1.1 Independent log-normal models fitted to respective NIVO+IPI and sunitinib datasets Justification Combination of best statistical fit and prior clinical input, after re-running survival analyses with the 30-month DBL. See #3 for explanation of why we prefer not to	Comment noted. The additional data cut provided by the company was considered by the Appraisal Committee at the second meeting. (Final Appraisal Determination Section 3.18)

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
					align with committee and ERG preferences for model selection.	
8	Consultee (company)	BMS	Utility regression model	30-month DBL data used. Justification Data availability; see Part 1.1. A regression model using utility values derived from the EQ-5D-3L data collected in CheckMate 214, with treatment arm, treatment status and progression status included as explanatory variables. Justification ACD 3.14: "*The company's preferred model assumed that people would have different utility values depending on their treatment arm and whether they were on treatment or not. The ERG considered that utility values would also depend on whether the disease had progressed. The committee considered it likely that disease progression would worsen quality of life and concluded progression-status should also be included in the regression model*."	30-month DBL data used. Justification Data availability; see Part 1.1. A regression model using utility values derived from the EQ-5D-3L data collected in CheckMate 214, with treatment arm, treatment status and progression status included as explanatory variables; specifically, Model 7 in Table 1. Justification Table 1's Model 7 is the best fitting model from the stepwise selection process followed, and aligns with the committee's stated preferences for analyses of these data.	Comment noted. The committee considered the additional health related quality of life data and agreed that progression status should be included in the model, however, it noted that the cost-effectiveness estimates were unlikely to be sensitive to the utility values used in the model. (Final Appraisal Determination Section 3.16)
9	Consultee (company)	BMS	Subsequent treatment	Subsequent treatment proportions as per CheckMate 214. Justification ACD 3.15: "*The committee concluded that, because all the analyses included the clinical benefits of the subsequent treatments in CheckMate 214, it preferred also to include the costs of those treatments.*"	Subsequent treatment proportions as per CheckMate 214. Justification Alignment with committee preferences.	Comment noted.

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10	Consultee (company)	BMS	Oral treatment administration	Administration costs applied for sunitinib and pazopanib <u>Justification</u> ACD 3.17: "*The ERG….included administration costs for treatment with sunitinib or pazopanib…The committee considered other changes* [including this] *to be reasonable*"	Administration costs applied for sunitinib and pazopanib <u>Justification</u> Alignment with committee preferences.	
11	Consultee (company)	BMS	Dosing approach for nivolumab maintenance	Dosing of nivolumab following the first four doses of NIVO+IPI amended to 480mg Q4W, with the first dose given 6 weeks after the last dose of nivolumab plus ipilimumab as per the draft SmPC. This dosing approach amendment also applied to second-line nivolumab monotherapy. <u>Justification</u> Though not considered as part of ACD deliberations, considered likely to be clinical practice if recommended, as described in the opening letter of this document, and therefore appropriate for decision making, at the committee's discretion.	Dosing of nivolumab following the first four doses of NIVO+IPI amended to 480mg Q4W, with the first dose given 6 weeks after the last dose of nivolumab plus ipilimumab as per the draft SmPC. This dosing approach amendment also applied to second-line nivolumab monotherapy. <u>Justification</u> Use of 480mg Q4W flat dosing will not only provide a significant benefit for patients by minimising the number of infusions, but also reducing nurse time and use of NHS resources to provide these infusions by half. It is expected that all patients treated with NIVO+IPI will be treated according to this new dosing schedule.	Comment noted. The Appraisal Committee considered the new dosing approach for nivolumab maintenance in their decision making (Final Appraisal Determination Section 3.14)
12	Consultee (company)	BMS	**Updated cost-effectiveness model and results** Table 3 and Table 4 show our interpretation of the updated committee and company base case, respectively; each as described in **Error! Reference source not found.**. While these results are deterministic, and as acknowledged, uncertain projections, both perspectives suggest that NIVO+IPI is a cost-effective option for NHS England patients with advanced, untreated RCC. In interpreting these results, we consider Section 3.22 of the ACD, where the committee note "*that in the company's economic model, people who are considered 'cured' because of an immunologic effect, do not receive a corresponding benefit to health-related quality of life compared to people whose disease had not yet progressed*" and that as a result "*The benefit of any immunological effect may not be fully captured in*			Revised base case results noted. N.B. The committee considered the equivalent results including the patient access schemes for subsequent treatments.

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the QALY calculation". With this in mind, the case for the committee to revise their ACD conclusions and recommend NIVO+IPI in this indication is compelling.

Table 3: January 2019 Committee-preferred deterministic base case cost-effectiveness results, based on stated and perceived committee preferences from Error! Reference source not found.
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>NIVO+IPI</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sunitinib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£39,911</td><td>1.38</td><td>2.65</td><td>£28,971</td></tr>
<tr><td>Pazopanib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£38,109</td><td>1.38</td><td>2.65</td><td>£27,663</td></tr>
<tr><td colspan="8">Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab with ipilimumab; QALY, quality-adjusted life years.</td></tr>
</table>

Table 4: Updated company base case pairwise incremental cost-effectiveness results
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>NIVO+IPI</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sunitinib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£38,838</td><td>3.51</td><td>1.64</td><td>£23,729</td></tr>
<tr><td>Pazopanib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£36,913</td><td>3.51</td><td>1.64</td><td>£22,552</td></tr>
<tr><td colspan="8">Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab with ipilimumab; QALY, quality-adjusted life years.</td></tr>
</table>
</td><td></td></tr>
<tr><td>13</td><td>Consultee (company)</td><td>BMS</td><td>Additional perceived misrepresentations and inaccuracies
As expressed in our opening letter, we found the ACD to be clear. We also found the ACD to be accurate, with only minor, but sometimes important, exceptions to this finding. Beyond what is stated</td><td>Comment noted. The Final Appraisal Determination has been updated to</td></tr>
</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
			in Part **Error! Reference source not found.**, we are minded to cite to only two sections of ACD text here. First, Section 3.10. The ACD states, "*The company considered in its base case that, because of the immunomodulatory mechanisms of nivolumab, a proportion of people who have nivolumab would return to a mortality rate equal to that of the general population. This assumes that some people who have nivolumab with ipilimumab are effectively 'cured'. Specifically, the company assumed that half of people who get a 'durable' response seen in the latest CheckMate 214 data-cut would return to the general population mortality rate.*" With reference to **Error! Reference source not found.**, assumption category #1, this is incorrect. In a cohort-level model, we assume an uncertain probability of an immunomodulatory survival effect. Though in application, the difference may not seem important, conceptually, in the minds of decision-makers, we feel that the distinction is important. Second, Section 3.21 of the ACD concludes that NIVO+IPI does not meet end-of-life criteria, considering "*that it would be inappropriate to apply special discretion at this time because survival data from CheckMate 214 are immature and there is uncertainty whether the life expectancy of people who would take nivolumab with ipilimumab in UK clinical practice differs from the source of the estimates*". We respect the right of the committee to apply discretion where the committee consider it reasonable, but struggle to reconcile the cited rationale with the decisions another committee (Committee C) applied to end-of-life weights in the recent appraisals of two chimeric antigen receptor T-cell therapies with highly immature survival data and highly limited, non-randomised comparator data (NICE ID1115 and NICE ID1166).	clarify probability of immunomodulatory survival effect (Section 3.10) Comment noted. The Appraisal Committee considered evidence from the CheckMate 214 trial to be most appropriate although not robust. (Section 3.20)
14	Consultee (company)	BMS	**References** 1. McDermott DF, Rini BI, Motzer RJ, et al. Treatment-Free Survival Following Discontinuation of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma: CheckMate 214 Analysis. European Society for Medical Oncology 2018 Congress. Munich, Germany. 19-23 October 2018. 874P. 2. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Company additional evidence submission 2018. (Updated: 17 December 2018). Accessed: 17 December 2018. 3. European Medicines Agency. OPDIVO: Procedural steps taken and scientific information after the authorisation. 2018. Available at: https://www.ema.europa.eu/documents/procedural-steps-after/opdivo-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed: 2 January 2018. 4. Bristol-Myers Squibb Pharmaceutical Limited. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion. 2018. 5. Bristol Myers Squibb. Clinical Protocol CA209214: A Phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma. 13 November 2018. Data on file.	References noted.

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
			6. Bristol-Myers Squibb. NHS oncologist nivolumab + ipilimumab in renal cell carcinoma model validation meeting report. December 2017. Data on file. 7. National Institute for Health and Care Excellence (NICE). TA417: Nivolumab for previously treated advanced renal cell carcinoma: Final Appraisal Determination: Committee papers. 2017. (Updated: 21 October 2016) Available at: https://www.nice.org.uk/guidance/ta417/documents/committee-papers-2. Accessed: 21 November 2017. 8. National Institute for Health and Care Excellence (NICE). TA483: Nivolumab for previously treated squamous non-small-cell lung cancer: Appraisal committee papers 2. 2017. (Updated: 1 November 2017) Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-5. Accessed: 3 January 2018. 9. National Institute for Health and Care Excellence (NICE). TA484: Nivolumab for previously treated non-squamous non-small-cell lung cancer: Appraisal Committee papers 3. 2017. (Updated: 01 November 2017) Available at: https://www.nice.org.uk/guidance/ta484/documents/committee-papers-6. Accessed: 10 January 2019. 10. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Committee papers. 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10189/documents/committee-papers. Accessed: 10 January 2019.	
1	Commentator	Novartis	No comment	Response noted.
1	Consultee (professional group)	NCRI-ACP-RCP-RCR	We believe the committee has failed to take into account relevant clinical evidence and has not come to a reasonable summary of the clinical effectiveness of this immunotherapy combination. The practice changing impact of ipilimumab + nivolumab in RCC reflects the induction of durable benefit with immunotherapy. Our experts were surprised that the ERG came to the conclusion that there was no evidence of durable benefit. This is untenable and ignores the following evidence: • Nivolumab single agent as a second and subsequent line of therapy in RCC has been approved by NICE following acceptance of evidence of durability of benefit. McDermott et al (Abstract 4507, ASCO 2016) demonstrated a plateau in survival curve due the immunological effect beyond 4 years in pooled data from phase I and II studies. • The phase 1 Checkmate 016 study (Hammers et al Journal of Clinical Oncology 35, (34) 2017 3851-3858) treated 3 cohorts of RCC patients including 47 patients with the ipilimumab 1mg/kg + nivolumab 3mg/kg schedule that was used in the Checkmate 214 registration study. Half of these patients had received previous therapy and would therefore not be expected to do as well as untreated patients. The PFS curve starts to plateau at 2 years and the median follow-up was 22.2 months. This study was updated by Plimack et al at the EIKCS meeting in 2017 with 37.7 month median follow-up (poster submitted to you by BMS). The updated PFS curves show durability beyond 2 years with a marked plateau beyond 3 years. Checkmate 016 was not adequately discussed in the ERG submission and no attempt was made to include the updated data which is in the public domain.	Comment noted. The ERG concluded that the explicit modelling of a durable benefit was modelled inappropriately (Final Appraisal Determination Section 3.11). The committee agreed that an extended survival benefit was possible but noted the lack of robust evidence on the size of the association between a clinically meaningful definition of response and long-term survival for nivolumab with

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 Checkmate 214 data has been updated with 30 month follow up and we understand has been submitted to the committee. This data confirms durability of PFS with a robust plateau on the Kaplan Meier curve for PFS.	ipilimumab. (Final Appraisal Determination Section 3.10).
3.1	Consultee (professional group)	NCRI-ACP-RCP-RCR	**'There were currently no data available to estimate the expected proportion of people this would apply to (cure)'.** This is inaccurate because of the data described above. It is entirely reasonable, indeed conservative, to assume that 15% of patients will be cured when treated with first line ipilimumab + nivolumab.	The committee considered that the Cancer Drugs Fund could be used to resolve clinical uncertainty surrounding this issue. (Section 3.10 and 3.26 of the Final Appraisal Determination)
3.2	Consultee (professional group)	NCRI-ACP-RCP-RCR	**'The ERG considered that the immunological effect should be removed entirely because there was no supporting evidence'.** Our experts are concerned about this summary of the ERG analysis and are concerned that the committee has been misled by an ERG appraisal that entirely ignores a) Nivolumab durability of benefit in second line treatment of metastatic RCC b) Mode of action of ipilimumab + nivolumab c) Updated Checkmate 016 data d) Durability of benefit with less active immunotherapies in RCC (IL-2 and IFN) For an ERG to come to the conclusion that no patients would experience durable benefit with immunotherapy betrays a lack of understanding of both the disease and the data. NICE should be able to have confidence in the quality of an ERG assessment. Unfortunately, this assessment falls well short of the standards one would expect. The ERG proposed that the investigator response assessment be used in preference to independent central review because their view was that in clinical practice it would be investigators making assessments of response. This surprising suggestion is at odds with accepted standards of trial design. The ERG's statement that Checkmate 016 'does not include any data on relevant comparators' is inaccurate. A phase I study would not be expected to have a standard arm comparator. The value of Checkmate 016 is as an older dataset with longer follow up which demonstrates durability of benefit in RCC patients treated with ipilimumab and nivolumab.	Comment noted. The ERG concluded that the explicit modelling of a durable benefit was modelled inappropriately (Final Appraisal Determination Section 3.11)
3.21	Consultee	NCRI-ACP-	**'The committee agreed that, for the combined poor- and intermediate-risk group, there was no robust**	Comment noted.

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	(professional group)	RCP-RCR	**evidence that average life expectancy was less than 24 months'.** Heng et al, Lancet Oncology 2013 demonstrated that the median OS of patients in the intermediate risk group was 22.5 months and 7.5 months in the poor risk group. Median OS for patients in the intermediate and poor prognostic groups in the Checkmate 214 study who were randomised to receive sunitinib was 18 months. There is no doubt that the outcome for patients with intermediate and poor prognosis RCC satisfies criteria for end-of life treatment. We do not understand why the committee and ERG have stated otherwise and assume this is an error in data interpretation.	The committee was presented with evidence from the CheckMate 214 trial that showed the median overall survival in the sunitinib arm was 25.9 months for the poor/intermediate risk group. (Final Appraisal Determination Section 3.20)
3.3	Consultee (professional group)	NCRI-ACP-RCP-RCR	There is no mention of the fact that although TKIs are a current standard of care for intermediate and poor prognosis RCC, they do not result in durable disease control for the vast majority of patients. TKIs are given with relatively short term palliative intent. Combination immunotherapy is given with the intent of gaining long term disease control.	Comment noted.
3.7	Consultee (professional group)	NCRI-ACP-RCP-RCR	**'Results uncertain because data immature with a median follow-up of 25.2 months, and only 32.9% of people having nivolumab with ipilimumab had died'.** This would appear to be irrelevant as the committee had already concluded that PFS was the appropriate primary endpoint measure. As an expert body of medical oncologists with specialist experience in the treatment of RCC we believe that ipilimumab + nivolumab is practice changing and is a new standard of care for the first line treatment of metastatic intermediate and poor risk RCC. This combination will confer durable benefit for at least 15% of the treated population. We urge the committee to reverse the ACD decision and to approve ipilimumab + nivolumab for the indicated metastatic RCC population.	Comment noted. The committee considered the overall survival data to be immature (Final Appraisal Determination Sectioon 3.7). The CheckMate 214 trial had co-primary endpoints of progression-free survival, overall survival and response rate.
1	Consultee (patient group)	KCSN	Nivolumab plus ipilimumab is the first immunotherapy combination proven to be a clinically effective and well-tolerated treatment for untreated advanced renal cell carcinoma (RCC), and has been granted priority review status by the US Food and Drug Administration (FDA). The combination was	Comment noted.

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			approved for use by the FDA in April 2018 and is heralded as a breakthrough treatment for untreated advanced RCC. The European Association of Urology (EAU) guidelines have been updated to recommend the use of the nivolumab plus ipilimumab combination as a frontline standard of care for intermediate- and poor-risk patients with untreated advanced RCC.	
2	Consultee (patient group)	KCSN	The nivolumab plus ipilimumab combination is well tolerated, and has proven to be more effective at extending progression-free survival and improving overall response rates in intermediate- and poor risk patients compared to standard first-line treatment with sunitinib. Adding the nivolumab plus ipilimumab combination as a choice in the first-line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life. The improved tolerability of the nivolumab plus ipilimumab combination enhances quality of life and enables patients to contribute socially and economically to society.	Comment noted.
3	Consultee (patient group)	KCSN	The committee's decision not to recommend first-line nivolumab plus ipilimumab was based upon the fact that the combination did not meet the end-of-life criteria for a combined population of intermediate- and poor-risk patients, and it is uncertain whether the survival benefit would be maintained in the long-term. However, this model is based upon data from clinical trials, which do not necessarily reflect routine clinical practice. Kidney Cancer Support Network (KCSN) urge NICE to consider funding for the combination through the Cancer Drugs Fund (CDF) to enable collection of real world survival data for intermediate- and poor-risk patients, which could potentially impact the final recommendation.	Comment noted. The recommendation has changed since the appraisal consultation document was issued and nivolumab with ipilimumab is now recommended for use within the Cancer Drugs Fund.
4	Consultee (patient group)	KCSN	We are disappointed that this innovative and clinically effective treatment for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer): Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families.	Comment noted.
5	Consultee (patient group)	KCSN	The nivolumab plus ipilimumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC; however, further efficacy data are required to determine the use of the combination for this cohort of patients. KCSN urge NICE to reconsider the combination for the CDF while further survival data are collected from the cohort of patients with non-clear cell RCC to provide evidence to support this unmet need.	Comment noted. The recommendation has changed since the appraisal consultation document was

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				issued and nivolumab with ipilimumab is now recommended for use within the Cancer Drugs Fund.
6	Consultee (patient group)	KCSN	The committee's decision to not recommend the nivolumab plus ipilimumab combination for untreated advanced intermediate- or poor-risk RCC patients denies terminally ill kidney cancer patients access to innovative and effective treatment within NHS England, despite the drug being available for kidney cancer patients living in the US and other European countries. This is confusing for the patient community because the committee has acknowledged the fact that the combination is effective, but recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those directly affected by their decision.	Comment noted.
7	Consultee (patient group)	KCSN	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.	Comment noted.
8	Consultee (patient group)	KCSN	In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and without the nivolumab plus ipilimumab combination, the clinician's choice of treatment is seriously compromised in the first-line. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.	Comment noted.
9	Consultee (patient group)	KCSN	Refusal of the nivolumab plus ipilimumab combination will force clinicians to prescribe a less effective first-line treatment for intermediate- and poor-risk advanced RCC, such as a tyrosine kinase inhibitor, which both they and their patients know has a poor side-effect profile and could negatively impact quality of life. In the worst-case scenarios, patients could be left without active treatment to face a premature death.	Comment noted.
10	Consultee (patient group)	KCSN	Current first-line treatment options are not effective for everyone. Unjustifiable restrictions in accessing the nivolumab plus ipilimumab combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.	Comment noted.
11	Consultee	KCSN	Nivolumab plus ipilimumab clinical trials have been conducted in untreated advanced RCC patients in	Comment noted.

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	(patient group)		the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of first-line nivolumab plus ipilimumab on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.	
12	Consultee (patient group)	KCSN	Now that the European Medicines Agency (EMA) has approved the nivolumab plus ipilimumab combination, the treatment is available to patients who have private health insurance or who can afford a private prescription, thus creating two-tier access for patients. The NICE appraisal process, therefore, disadvantages less affluent patients, who rely on NHS England to care for them in the later stages of their lives.	Comment noted.
1	Commentator (Web comment)	Ipsen	We note from the Committee papers that NHS England have proposed a probable treatment pathway following the introduction of nivolumab + ipilimumab in intermediate-/poor-risk patients. It is not clear whether this proposal is to make nivolumab + ipilimumab the only available treatment in 1st line for intermediate-/poor-risk patients, or an available treatment. It remains the case that some patients will be contraindicated for immunotherapy or will not wish to take it. It is, therefore, important that the other NICE-approved, cost-effective first-line treatments remain available.	Comment noted. The NICE-approved treatments will remain treatment options at first line.
1	Commentator (Web comment)	NHS professionals	Supports above statements from NCRI-ACP-RCP-RCR.	Please see NICE responses above.
1	Consultee (company)	BMS CDF proposal	**Executive summary** **Commercial arrangement:** NHS England (NHSE) shall be entitled to an overall discount of [redacted]% (or [redacted]% after value added tax [VAT]-adjustment) on nivolumab for this indication. **Data collection arrangement:** The data collection would be anticipated to conclude in either August 2020 or 2021, when it is expected that the 5-year and 6-year follow-up data respectively will be available from the CheckMate 214 trial.	Comments noted. The recommendation has changed since the appraisal consultation document was issued and nivolumab with ipilimumab is now recommended for use within the Cancer Drugs Fund.
2	Consultee (company)	BMS CDF proposal	**Introduction** This document provides details of the commercial and data collection arrangement being proposed by	Comments noted.

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			Bristol Myers Squibb (BMS) as part of this appraisal. This offering is designed to ensure that patients have access to this important new treatment while data are collected which will address the Committee's concerns highlighted in the second Appraisal Committee Meeting (ACM) and subsequent discussions between the National Institute for Health and Care Excellence (NICE), NHSE and BMS. The feedback from the ACM on the 22nd January is the Committee has uncertainty in the long-term survival of patients on NIVO+IPI which has an impact on the cost-effectiveness of NIVO+IPI. In this proposal we present analyses using different parametric extrapolations along with a commercial scheme to manage the uncertainty. These analyses result in ICERs for NIVO + IPI versus sunitinib between £20,885 and £26,307 which are all below the £30,000 per quality-adjusted life year (QALY) threshold. This greatly reduces the risk to NICE and NHSE from approving this indication for use. Furthermore, the provision of 5- or 6- year data for this indication will significantly reduce the uncertainty regarding the long-term efficacy of NIVO+IPI, and provide a unique opportunity to characterise the long-term survival of NIVO+IPI in this indication.	
3	Consultee (company)	BMS CDF proposal	**Unmet need in untreated advanced renal cell carcinoma** There remains a significant unmet need for patients who have untreated advanced renal cell carcinoma. Patients with advanced RCC have a life-threatening condition and face a worsening life expectancy with increasing adverse prognostic factors. Standard first-line management in the NHS is currently restricted to systemic VEGFR tyrosine kinase inhibitor agents that have no proven significant benefit on OS, and can be associated with significant toxicity.[1-4] There is a clear unmet need for new treatment modalities to improve physician and patient choice and potentially improve the life expectancy of patients. NIVO+IPI is the first immunotherapeutic agent licensed for use in first-line advanced RCC and thus represents a 'step-change' in the management of this disease for patients. In intermediate-/poor-risk patients (a population with the highest unmet medical need and most severe prognosis), NIVO+IPI has clearly shown the potential to significantly improve life expectancy and quality of life for those with untreated advanced RCC	Comments noted.

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4	Consultee (company)	BMS CDF proposal	**Revised commercial arrangement** BMS understand that the Appraisal Committee have concerns about the cost-effectiveness of NIVO+IPI given the potential range of incremental cost-effectiveness ratios (ICERs) resulting from the different OS extrapolation methods used. Given the preference of the Committee to consider ICERs both from analyses using the ERG's more conservative survival modelling approach (Kaplan–Meier [KM] followed by extrapolation of select KM data using the exponential function) and from the company approach (extrapolation using the entirety of the KM data, with a log-normal curve chosen based on the best statistical fit), BMS are willing to offer an increased confidential commercial discount to ensure that the plausible ICERs for NIVO+IPI are below a £30,000 per QALY gained willingness-to-pay threshold. The commercial scheme will be administered directly with NHS England as a confidential rebate on the acquisition of nivolumab as part of NIVO+IPI treatment (induction and maintenance phases) for intermediate-/poor-risk patients with untreated advanced renal cell carcinoma. In addition to the agreed NHS price reduction of [redacted]% for nivolumab in all indications, NHS England shall be entitled to receive a rebate of [redacted]% on the invoiced spend (equivalent to an overall discount of [redacted]% or [redacted]% after VAT adjustment, **Table 5**) of nivolumab for this indication. The rebate will be based on the number of vials used for untreated advanced RCC in intermediate-/poor-risk patients in addition to the confidential NHS discount price. All rebates will include a VAT 'true-up' – calculation of this amount is provided in Table 5. Table 5: **Calculation of VAT 'true-up' for nivolumab for untreated advanced renal cell carcinoma in intermediate-/poor-risk patients using 4-ml vial** 	Comments noted.
5	Consultee	BMS CDF	**Revised ICERs**	Revised ICERs

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	(company)	proposal	The revised commercial proposal is based on the ERG's preferred economic assumptions, as presented in Tables 5 and 6 of the ERG Addendum, dated 18th January 2019.[5] As the committee consider the OS extrapolation method used by the ERG (KM data plus exponential without any patients reaching general population mortality risk) to be conservative (Appraisal Consultation Document [ACD] 3.10)[6], analyses are presented below using a range of OS extrapolation methods. Cost-effectiveness results using extrapolation with log-normal and log-logistic treatment-independent curves (using the entirety of the CheckMate 214 OS data) are also presented. Log-normal and log-logistic curves both fit the data well according to Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, and meet the expectations of clinicians interviewed for the company submission (5-year OS between 35% and 45% for NIVO+IPI).[7] Log-normal and log-logistic extrapolations have decreasing hazards over time, resulting in approximately 15% of NIVO+IPI patients and 5% and 6% of sunitinib (and pazopanib) patients receiving general population mortality risk (as the model is programmed to ensure probability of death can be no lower than the average for the age-adjusted general-population), respectively. As preferred by the Committee, the analyses shown do not include any treatment stopping rules or any explicit modelling of long-term immunotherapeutic survival benefit from response to NIVO+IPI or subsequent nivolumab monotherapy beyond the standard parametric survival model extrapolations limited by general population mortality. The ICERs using the Committee's preferred economic assumptions for the current patient access scheme (PAS) and the proposed commercial scheme with the revised rebate applied for nivolumab, are presented in Table 6. Results using a log-normal and log-logistic extrapolation for OS are shown in Table 7 and Table 8, respectively. The results in Table 6 to Table 8 show that when using the proposed Cancer Drug Fund (CDF) commercial scheme, NIVO+IPI is cost-effective across analyses using a range of different OS extrapolations, with all ICERs below £30,000 per QALY gained, even in the absence of any immunotherapeutic survival assumptions for durable responders. **Table 6: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the ERG Addendum, dated 18th January 2019), using KM plus exponential for OS extrapolation** **Technologies** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER, NIVO+IPI versus (£/QALY)** **Current baseline commission patient access scheme ([redacted]%)**	were considered by the Appraisal Committee.

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NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£39,699	1.05	£37,694
Pazopanib	[redacted]	[redacted]	£37,774	1.05	£35,866
Proposed CDF commercial scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£27,706	1.05	£26,307
Pazopanib	[redacted]	[redacted]	£25,781	1.05	£24,479

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 7: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the ERG Addendum, dated 18th January 2019), using log-normal for OS extrapolation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER, NIVO+IPI versus (£/QALY)
Current baseline commission patient access scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£41,375	1.41	£29,410
Pazopanib	[redacted]	[redacted]	£39,449	1.41	£28,042
Proposed CDF commercial scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£29,381	1.41	£20,885
Pazopanib	[redacted]	[redacted]	£27,456	1.41	£19,517

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 8: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
ERG Addendum, dated 18th January 2019), using log-logistic for OS extrapolation
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER, NIVO+IPI versus (£/QALY)</th></tr>
<tr><td colspan="6">Current baseline commission patient access scheme ([redacted]%)</td></tr>
<tr><td>NIVO+IPI</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Sunitinib</td><td>[redacted]</td><td>[redacted]</td><td>£40,273</td><td>1.19</td><td>£33,792</td></tr>
<tr><td>Pazopanib</td><td>[redacted]</td><td>[redacted]</td><td>£38,348</td><td>1.19</td><td>£32,177</td></tr>
<tr><td colspan="6">Proposed CDF commercial scheme ([redacted]%)</td></tr>
<tr><td>NIVO+IPI</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Sunitinib</td><td>[redacted]</td><td>[redacted]</td><td>£28,279</td><td>1.19</td><td>£23,729</td></tr>
<tr><td>Pazopanib</td><td>[redacted]</td><td>[redacted]</td><td>£26,354</td><td>1.19</td><td>£22,113</td></tr>
</table>
Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.
</td><td></td></tr>
<tr><td>6</td><td>Consultee (company)</td><td>BMS CDF proposal</td><td>
Data collection proposal

1 Purpose of data collection proposal

The purpose of this data collection proposal is to outline how BMS propose to address the Committee’s existing concerns with longer-term data from its existing clinical trial package for NIVO+IPI.

2 Proposed commencement and period of agreement

This proposed data collection arrangement would take effect on publication of the managed access agreement. The data collection would be anticipated to conclude in either August 2020 or 2021, when it is expected that the 5-year and 6-year follow-up data respectively will be available from the CheckMate 214 trial.
</td><td>Comments noted. The Data collection proposal was considered by the Appraisal Committee in its considerations for recommendation through the CDF.</td></tr>
</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

3 Anticipated patient eligibility

If NIVO+IPI were recommended for use in the CDF, it is anticipated that key patient eligibility criteria for NIVO+IPI's use in the Cancer Drugs Fund would be aligned to the licensed indication. These will be determined by NHS England in consultation with NICE and BMS.

4 Area(s) of clinical uncertainty

The long-term overall survival was a key area of uncertainty identified by the NICE committee. The primary source of data to address these will be the ongoing trial described under bullet 5 below.

5 Source(s) of data collection

Data collection from the ongoing clinical trial (CheckMate 214) will be the primary source of data collection. A 5-year data cut from the CheckMate 214 trial is expected in August 2020 with a 6-year data expected in August 2021. Table 9 provides a brief description of the trial.

Clinical trial

As per the most recent database lock (6 August 2018), there are [redacted] in follow-up or still on treatment in the CheckMate 214 trial. Based on lognormal or KM plus exponential OS extrapolations from the economic model, we anticipate between [redacted] and [redacted] or [redacted] and [redacted] patients will be in follow up or still on treatment at 5 and 6 years respectively.

Table 9: CheckMate 214 overview

CheckMate 214 – Phase III study (n=1390)
Description: Multicentre, open-label, randomised phase III study, with nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg solutions IV Q3W for 4 doses then nivolumab 3 mg/kg solutions IV Q2W
Primary Endpoint: IRRC-assessed ORR and PFS, and OS, in intermediate-/poor-risk subjects with previously untreated advanced or metastatic RCC
Secondary Endpoints: IRRC-assessed ORR and PFS, and OS, in any-risk subjects with previously untreated RCC. Incidence of AEs in all treated subjects with previously untreated advanced or metastatic RCC
Exploratory Endpoints: Overall safety and tolerability of NIVO+IPI versus sunitinib. IRRC-assessed ORR

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
			and PFS, and OS in favourable-risk subjects with previously untreated advanced or metastatic RCC. Explore potential predictive biomarkers of clinical response by analyzing tumor specimens and blood samples for proteins and genes involved in regulating immune responses. Evaluate HRQoL as assessed by FACT-G. Assess disease related symptoms in each arm based on NCCN FKSI-19. Assess changes in global health status based on EuroQol's EQ-5D. **Abbreviations:** AE: adverse event; EQ-5D: EuroQoL 5-Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-19: Functional Assessment of Cancer Therapy-Kidney Symptom Index; HRQoL: health-related quality of life; IRRC: Independent radiological review committee; IV: intravenous; NCCN; National Comprehensive Cancer Network: NIVO+IPI; nivolumab plus ipilimumab; ORR: Overall Response Rate, OS: Overall Survival, PFS: Progression free survival, Q2W: every 2 weeks, Q3W: every 3 weeks, RCC: renal cell carcinoma. ***SACT*** 5.1 The Systemic Anti-Cancer Therapy (SACT) dataset is a mandated dataset as part of the Health and Social Care Information Standards. Data can also be collected via the SACT dataset during the data collection arrangement period, specifically: • Overall survival • Duration of therapy **6 Outcome data to be collected** ***Clinical trial*** 6.1 The most pertinent outcome to be measured is long-term overall survival. At the end of the data collection period, data will be available from the ongoing CheckMate 214 trial. This will be supplemented by the data collected in SACT. ***SACT*** 6.2 Data collection via SACT will support data collected in the clinical trial. During the managed access agreement period, SACT will collect data on overall survival and duration of treatment.	

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
			7 Proposed data analysis plan 7.1 Analyses will be provided for NIVO+IPI for untreated advanced RCC in patients with intermediate-/poor-risk from the ongoing clinical trial and SACT.	
7	Consultee (company)	BMS CDF proposal	**References** 1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007; 356(2):115-24. 2. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind Phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European Journal of Cancer. 2013; 49(6):1287-96. 3. Schmidinger M. Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. EJC Suppl. 2013; 11(2):172-91. 4. Ravaud A. Treatment-associated adverse event management in the advanced renal cell carcinoma patient treated with targeted therapies. Oncologist. 2011; 16 Suppl 2(Suppl 2):32-44. 5. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Appraisal consultation document. 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10189/documents/appraisal-consultation-document. Accessed: 5 February 2019. 6. Liverpool Reviews and Implementation Group (LRiG). Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID 1182]: Addendum. 18 January 2019. Not yet published. 7. Bristol-Myers Squibb. NHS oncologist nivolumab + ipilimumab in renal cell carcinoma model validation meeting report. December 2017. Data on file.	References noted.

Bristol-Myers Squibb Response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document – Nivolumab with ipilimumab for untreated advanced renal cell carcinoma [ID1182]

January 2019

Dear Helen,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for nivolumab with ipilimumab (NIVO+IPI) for untreated advanced renal cell carcinoma (RCC) [ID1182].

Has all of the relevant evidence been taken into account?

When the ACD was published, the committee had not seen results from a cost-effectiveness analysis using its preferred assumptions (as acknowledged in Section 4.17 of the ACD). Our ACD response provides the committee with this updated analysis, including survival analysis updated with 30-month CheckMate 214 data, updated dosing assumptions to reflect the anticipated uptake of Q4W dosing for nivolumab, and scenario analyses for treatment stopping rules.

In Section 3.7 of the ACD, the committee note that the survival data from the interim analysis database-lock (DBL) supporting the company submission (CS) were immature (7 August 2017, minimum follow-up 18 months, “18-month DBL”). In the period prior to the Committee for Medicinal Products for Human Use (CHMP) decision in November 2018, treatment-free survival data from an updated DBL (6 August 2018, minimum and median follow-up of 30 and [redacted] months, respectively, “30-month DBL”) were disseminated at the European Society for Medical Oncology (ESMO) 2018 Congress.[1] [redacted]. We incorporated 30-month DBL data into the updated analyses provided to NICE in December 2018 (ID1182 Company additional evidence submission).[2] This data is incorporated within the results presented herein wherever possible.

The original company base case used 3mg/kg Q2W dosing for nivolumab during the maintenance phase of treatment, as per the CheckMate 214 trial dosing. However, the European Medicines Agency has since introduced new variations to the nivolumab packet leaflet and SmPC to update the dosing schedule of nivolumab, replacing weight based dosing with 240mg Q2W flat dosing for all previously licensed indications or 480mg Q4W flat dosing for melanoma and previously treated RCC indications.[3] The draft SmPC including the untreated advanced RCC indication has included this dosing regimen.[4] Use of 480mg Q4W flat dosing will not only

provide a significant benefit for patients by minimising the number of infusions, but also reduces the nurse time and NHS resources to provide these infusions by half. It is expected that all patients treated with NIVO+IPI will be treated according to this new dosing schedule.

In Section 3.11 of the ACD, the committee note that it is not appropriate to include a stopping rule, because they had not been presented with evidence exploring the impact of a stopping rule on clinical outcomes. Although we believe that a 2- or 5-year stopping rule would not impact clinical outcomes, scenario analysis using varying probabilities of immunologic effect, 2- and 5-year treatment stopping rules and treatment waning effects for the company and committee base case analyses were presented in Tables 1-4 of the December 2018 “ID1182 Company additional evidence submission” document.[2]

Given the updated clinical effectiveness data and dosing regimen, BMS believe that the committee would benefit from inviting one or more independent clinical and patient experts to the second appraisal committee meeting (ACM).

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

While we feel the summaries of clinical and cost effectiveness are reasonable and provide clear interpretations of the evidence that was available to the committee at time of writing, we note some misrepresentations and inaccuracies, which we document in this response.

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

Given the evidence now available that could not be taken into account at the time, and to a lesser extent the misinterpretations and inaccuracies we have observed in the ACD, we do not believe the current ACD recommendations are a sound and suitable basis for guidance to the NHS.

Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?

We do not believe so.

Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?

We do not believe so.

The remainder of this response comprises two parts. Part 1 presents additional evidence from the 30-month DBL of CheckMate 214, cost-effectiveness analyses informed by these data and what we interpret to be the committee's preferred base case assumptions, as well as separately, cost-effectiveness analyses informed by these data and our preferred assumptions. Part 2 discusses perceived misrepresentations and inaccuracies in the ACD not covered in Part 1.

From the evidence provided within our updated analyses[2] and in this response document, we trust a positive recommendation for NIVO+IPI for untreated advanced RCC will be issued following the second ACM.

Yours sincerely,

Chris Kiff

HEOR Manager, Bristol-Myers Squibb Pharmaceutical Ltd

1. Additional evidence, analyses and core comments

1.1. 30-month DBL CheckMate 214 data

Clinical effectiveness data

Figure 1 shows CheckMate 214 30-month DBL OS data in the form of Kaplan–Meier (KM) curves, alongside the CS-preferred and committee-preferred OS extrapolations, based on 18-month DBL data. Also shown in Figure 1: time to subsequent therapy of death KM curves based on the 30-month DBL, as presented at ESMO 2018.[1]

Figure 1: Extrapolation of CheckMate 214 OS data using the 7 August 2017 database lock compared to KM plots from 6 August 2018 and time to subsequent therapy or death from McDermott et al.[1]*

Key: KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.
Notes: Time to subsequent therapy or death KM data were digitised from McDermott et al. Other KM data are based on patient-level data from the CheckMate 214 August 2018 database lock.
* zero IO survival effect assumed for “Committee” curves, which is not in line with committee preferences, as stated in ACD Section 3.17.

Figure 1 highlights two key implications of the 30-month DBL OS data. First, OS extrapolations for NIVO+IPI patients based on the 18-month DBL under-predict observed survival in the 30-month DBL. This is true for both the company-preferred (log-normal) and committee-preferred (KM + exponential) survival models.

Second, OS extrapolations for sunitinib patients based on the 18-month DBL under-predict observed survival in the 30-month DBL. Again, this is true for both the company-preferred (log-normal) and committee-preferred (KM + exponential) survival models, to a greater extent than for the NIVO+IPI patients. This is explained by the November 2017 trial protocol amendment, after the primary endpoint of the trial had been met, allowing patients on the sunitinib arm to crossover to the NIVO+IPI arm,[5] and illustrated by the time to subsequent therapy or death KM curves in Figure 1. Although approximately [redacted] of patients on the sunitinib arm are alive at 44 months, only 7% of patients on the sunitinib arm are alive and not on subsequent therapy. Nivolumab monotherapy was the most commonly received subsequent therapy on the sunitinib arm of CheckMate 214, with [redacted] of the [redacted] patients receiving subsequent therapy ([redacted]) receiving subsequent nivolumab as of the 18-month DBL. It is therefore likely that the majority of patients alive on the sunitinib arm at the latest data cut-off will have received NIVO+IPI or nivolumab monotherapy as a subsequent therapy.

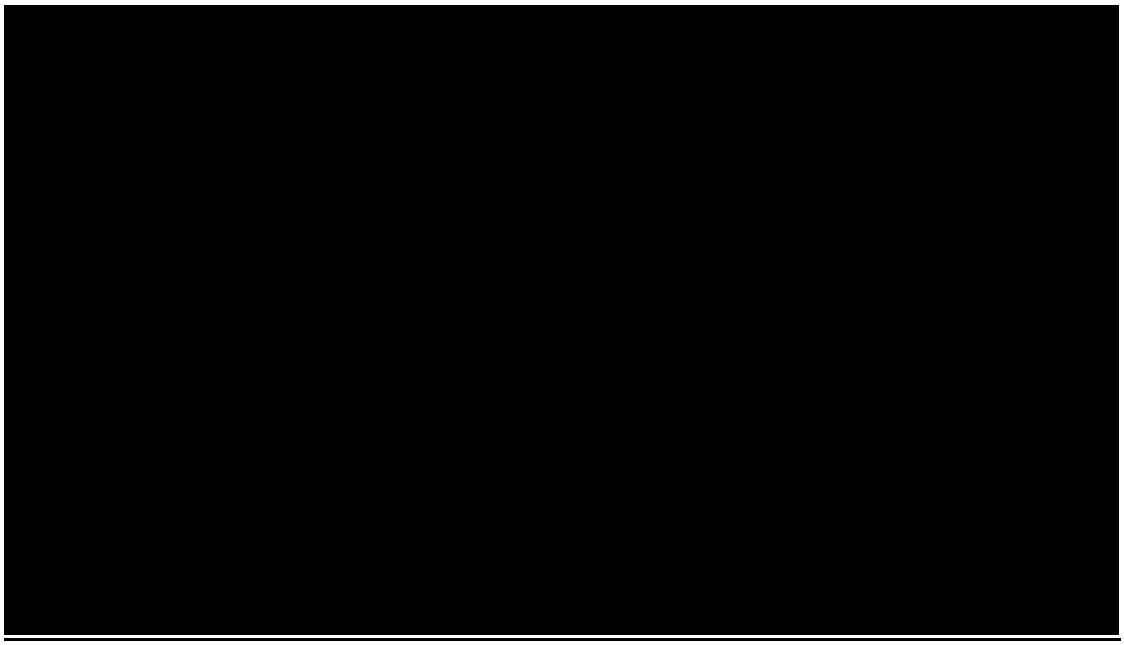
We performed survival analyses on 30-month DBL OS data and incorporated this into the economic model in order to provide the functionality to meet committee preferences, as per the economic model submitted alongside the “ID1182 Company additional evidence submission” document.[2] We were also able to do this for time-to-discontinuation (TTD) data and show committee-preferred (KM + exponential) model fits to these data in Figure 2. Alongside these curves in Figure 2 are the committee-preferred TTD models based on 18-month DBL data, the 30-month DBL OS KM data and committee-preferred (KM + exponential) extrapolations of these data and the 18-month DBL OS data.

The Aug-18 curves in Figure 2 represent the updated OS and TTD data informing updated committee-preferred cost-effectiveness results, presented in Part 1.2, with one caveat, also noted below Figure 1. In Section 3.17 of the ACD, the committee note, in divergence from the ERG’s preferences for analysis, that it may be

reasonable to include an immunological effect. We attempt to explicitly capture the committee's preferences on this point in Part 1.2, but here note that Figure 2 extrapolations do not include an immunologic effect. Instead, overall survival extrapolations including a range of immunologic effect probabilities using the committee preferences are shown in Figure 3.

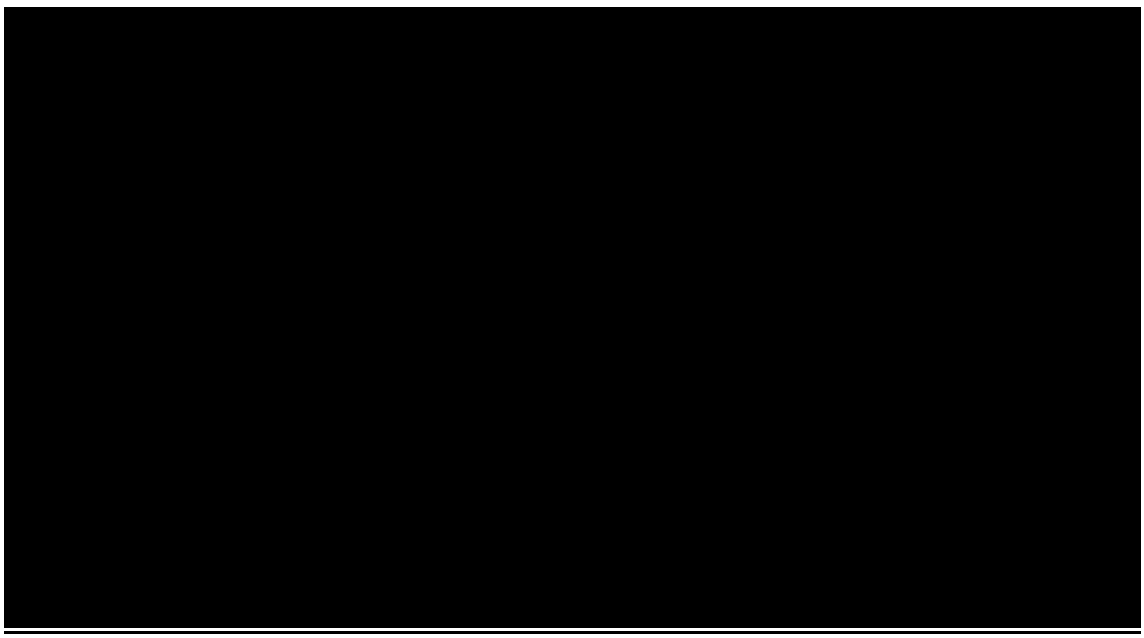
Section 3.17 of the ACD also notes the committee's preference for independent radiology review committee (IRRC)-assessed progression free survival (PFS) data, in contrast to the ERG's preference on this point. [redacted]. However, as the committee note in Section 3.18 of the ACD, cost-effectiveness results are less sensitive to PFS uncertainty than TTD and OS uncertainty. For this reason and for clarity, we have restricted the data presented in Figure 2 to TTD and OS data.

Figure 2: 30-month DBL OS and TTD KM data, extrapolated using committee-preferred assumptions*



Key: KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; TTD, time to discontinuation.
* zero IO survival effect assumed in Figure 2, which is not in line with committee preferences, as stated in ACD Section 3.17.

Figure 3: 30-month DBL OS KM data, extrapolated using committee-preferred assumptions and varying probabilities of immunologic effect occurring



Key: IO prob, probability of immunologic effect occurring; KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.

Health-related quality of life data

Section 3.14 of the ACD states the preference for disease progression to be included as a variable in the base case utility analysis. We have updated the analysis to align with the committee's preference. In our original analysis, we used the model without this variable in the CS on the basis of statistical goodness-of-fit, through the stepwise selection process described in Section B.3.4.1 of the CS.

We have updated our analysis of CheckMate 214 patient-reported EQ-5D-3L data using EQ-5D-3L data from the 30-month DBL. Table 1 shows parameter values and model fits from the stepwise variable selection process using the 30-month DBL data, and is analogous to Table 28 of CS Section B.3.4.1. The best fitting model in Table 1; Model 7; aligns with the committee's stated preferences for analyses of these data.

Table 2 shows the mean health state utility values implied by Model 7 of Table 1, alongside the mean health state utility values from the CS base case, for comparison. When interpreting these data, as for 30-month OS data, it is important to consider the likely impact of treatment crossover and subsequent nivolumab monotherapy for sunitinib arm patients in "off treatment" health states.

Table 1: Results from stepwise variable selection approach to mixed model analysis of CheckMate 214 intermediate-/poor-risk EQ-5D-3L utility data (6 August 2018 DBL)

	Estimate (SE), P-Value						
Parameters/Fit Statistics	**Model 1: intercept only**	**Model 2: add Treatment Arm**	**Model 3: add Progression Status**	**Model 4: add Treatment Status**	**Model 5: add Treatment Arm to Model 4**	**Model 6: add Progression Status to Model 4**	**Model 7: add Progression Status and interactions to Model 5**
Intercept	0.7616 (0.0068), <.0001	0.7790 (0.0096), <.0001	0.7671 (0.0069), <.0001	0.7740 (0.0069), <.0001	0.7938 (0.0097), <.0001	0.7734 (0.0069), <.0001	0.7933 (0.0097), <.0001
Treatment Arm (Sunitinib)		-0.0351 (0.0136), 0.0102			-0.0397 (0.0138), 0.0040		-0.0398 (0.0138), 0.0040
Progression Status (Progression)			-0.0343 (0.0052), <.0001			0.0052 (0.0072), 0.4700	0.0006 (0.0093), 0.9451
Treatment Status (Off treatment)				-0.0568 (0.0045), <.0001	-0.0679 (0.0066), <.0001	-0.0454 (0.0061), <.0001	-0.0441 (0.0092), <.0001
Treatment Arm*Progression Status							0.0092 (0.0146), 0.5289
Treatment Arm*Treatment Status					0.0208 (0.0091), 0.0220		-0.0024 (0.0124), 0.8462
Progression Status*Treatment Status						-0.0284 (0.0107), 0.0082	-0.0480 (0.0150), 0.0014
Treatment Arm*Progression Status*Treatment Status							0.0383 (0.0217), 0.0770
-2 Log Likelihood	-7441.7	-7448.2	-7484.4	-7597.9	-7609.7	-7605.8	-7624.3
AIC (smaller is better)	-7435.7	-7440.2	-7476.4	-7589.9	-7597.7	-7593.8	-7604.3
AICc (smaller is better)	-7435.7	-7440.2	-7476.4	-7589.8	-7597.7	-7593.8	-7604.3
BIC (smaller is better)	-7421.5	-7421.3	-7457.5	-7570.9	-7569.3	-7565.4	-7557

Key: AIC; Akaike information criterion; AICc, Akaike information criterion with a correction for small samples; BIC; Bayesian information criterion; SE, standard error.

Table 2: Comparison of utility values from regression analysis of the August 2017 and August 2018 DBLs

Database lock	NIVO+IPI		Sunitinib	
	Aug-17	**Aug-18**	**Aug-17**	**Aug-18**
PFS on treatment utility	0.793	0.793	0.751	0.754
PFS off treatment utility	0.719	0.749	0.699	0.707
PPS on treatment utility	0.793	0.794	0.751	0.763
PPS off treatment utility	0.719	0.702	0.699	0.707
Key: PFS, progression-free survival; PPS, post-progression survival				

1.2. Committee and company preferences

Data from the 30-month DBL of CheckMate 214 presented in Part 1.1, changes to the SmPC for nivolumab noted at the start of this document, and committee preferences clearly summarised in Section 3.17 of the ACD each have implications for the committee's preferred analysis. Table 3 summarises what we understand to be committee-preferred assumptions, by nine assumption categories, based on ACD statements wherever possible. The preferences are stated in terms of deviations from the CS base case, following ACD Section 3.17. Table 3 also summarises our current preferences by each assumption category. In the majority of cases, our current preferences align with committee preferences. Where they do not, we express our rationale for further consideration by the committee.

Table 3: January 2019 Committee preferences (as interpreted from evidence available) and company preferences, in terms of deviations from the CS base case, by assumption category.

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
1	Immunological effect	25% probability of immunological survival effect for durable responders only. <u>Justification</u> ACD 3.10: "*The committee concluded that the size of any immunological effect is highly uncertain and could lie somewhere between the company's optimistic [50%] and ERG's conservative assumptions [0%]*"	50% probability of immunological survival effect for durable responders only. <u>Justification</u> We recognise the high level of uncertainty here and in the CS. We have attempted to base our assumptions on as much evidence as possible. Clinical opinion was that this effect would only occur in those patients who have a durable response, and that these patients would be likely to experience a long-term survival benefit.[6] The proportion of patients from CheckMate 214 (CheckMate 025 for second-line nivolumab) who were experiencing a durable response was used to inform the proportion who could potentially experience a long-term immunological effect (as per the NICE technology appraisal for nivolumab monotherapy in previously treated RCC patients [TA417][7]). A model input for the probability of this effect was incorporated as an uncertain parameter; specifically, a 50% probability of an immunological survival effect being borne out is assumed. The probability of an IO effect remains unknown, but given clinical expectations and data available now, we do not believe our assumptions are implausible, or even necessarily optimistic. If such an effect is likely for durable responders, our approach is conservative.

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
2	Stopping rule	No stopping rule included. Justification ACD 3.11: "*it is not appropriate to include a stopping rule for decision-making*"	Patients are unlikely to receive nivolumab beyond 2 years and definitely not beyond 5 years. Justification We are open to the use of a stopping rule as part of the recommendation for NIVO+IPI use in untreated RCC. Confidence in a stopping rule and prolonged benefit of NIVO+IPI is demonstrated in [redacted] Scenario analysis using varying probabilities of IO effect, 2- and 5-year treatment stopping rules and treatment waning effects for the company and committee base case analyses were presented in Tables 1-4 of the December 2018 "ID1182 Company additional evidence submission" document.[2] Treatment waning effects were incorporated in this analysis, in a similar manner to those used in the NICE technology appraisals for nivolumab in previously treated squamous and non-squamous non-small-cell lung cancer.[8, 9]

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
			A treatment stopping rule is appropriate because patients will not receive any additional benefit from remaining on treatment, as the treatment has already worked, and the mechanism of action allows this benefit to continue, whether or not the patient remains on treatment. If this were not the case, treatment waning would occur if a patient discontinued treatment, making a stopping rule ethically problematic. Further, in their submission for this appraisal, NHS England note that "the majority of recent NICE recommendations have included 2 year stopping rules for anti-PD-1 and anti-PD-L1 drugs … there is therefore a clear trend in terms of NICE decision making but its acceptance by clinicians also reflects increasing clinical concern as to the longer term toxicities of such immunotherapy".[10] As such, we believe either a 2 or 5-year stopping rule would not affect the life year or QALYs gain expected for NIVO+IPI.
3	Time to discontinuation	30-month DBL data used. <u>Justification</u> Data availability; see Part 1.1. Assumed equivalence between sunitinib and pazopanib. <u>Justification</u> ACD 3.13: "*pazopanib and sunitinib are considered clinically equivalent….and time to stopping treatment for pazopanib and sunitinib should also be considered to be the same*"	30-month DBL data used. <u>Justification</u> Data availability; Part 1.1. Assumed equivalence between sunitinib and pazopanib. <u>Justification</u> Alignment with ACD 3.13. [redacted]

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
		KM followed by exponential curve to extrapolate the data. Justification ACD 3.16: "*The ERG considered that a piecewise model, where Kaplan–Meier data .. are followed by a parametric curve, was appropriate because the proportional hazards assumption was not met and in all the cumulative hazard plots, the curves were parallel at the start then separate. The ERG appended exponential curves to the Kaplan–Meier data because later portions of the cumulative hazard plots showed an exponential trend. The ERG chose 21 to 22 months to switch from Kaplan–Meier data to an exponential curve because after this time point there are few patients remaining, which makes the Kaplan–Meier data uncertain. The ERG note that the extrapolation is not sensitive to the time point chosen for the switch, because the shape of the exponential curve is defined by plotting a straight line on the cumulative hazard plot. The committee agreed that the cumulative hazard plots suggested that using the Kaplan–Meier, followed by an exponential curve, was appropriate to extrapolate the data*."	Justification As per CS, Section B.3.3. While we respect the committee's preferences, we question the appropriateness of using KM data followed by an exponential curve for extrapolation of survival outcomes, given NIVO+IPI's mechanism of action. RCC patients on nivolumab and sunitinib have been shown to have decreasing OS HRs over time, as commented by the ERG in Section 5.4.3 and Figure 8-10 of the ERG report, "[it is] *to be expected, as less fit patients will likely to die earlier than fitter patients and the patients left at risk will have lower mortality risk*". This is arguably truer for immuno-oncology therapies, which are expected to provide a great long-term survival benefit for those who respond to treatment. The cumulative OS hazard from the sunitinib global expanded access trial, the source with greatest number of patients and longest follow-up, shows a continual decrease in hazards, with a linear trend only observed after 30 months. The ERG and thus committee approach is to use a long-term exponential extrapolation for survival, based on the shape of the clinical trial log-cumulate hazards in the last few months of the 18-month data. Scant clinical rational or statistical analysis were used to select the point at which the exponential curve was applied.
4	Progression-free survival	Secondary-definition IRRC-assessed PFS data Justification	Secondary-definition IRRC-assessed PFS data Justification

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
		ACD 3.12: "*The committee noted investigator-assessed progression-free survival was not a primary outcome of CheckMate 214 and, being unblinded, it may introduce bias. The committee recalled that it considered progression-free survival results should include people who have subsequent treatment before progression ... The committee concluded that the IRRC-assessed progression-free survival results which included people who have subsequent treatment before progression should be used in the economic model.*" KM followed by exponential curve to extrapolate the data. Justification ACD 3.16: see #3	Alignment with ACD 3.12. Independent cubic spline 2-knots hazard models fitted to respective NIVO+IPI and sunitinib datasets Justification Combination of best statistical fit and prior clinical input, [redacted]. See #3 for explanation of why we prefer not to align with committee and ERG preferences for model selection.
5	Overall survival	30-month DBL data used. Justification Data availability; see Part 1.1. KM followed by exponential curve to extrapolate the data. Justification ACD 3.16: see #3	30-month DBL data used. Justification Data availability; see Part 1.1 Independent log-normal models fitted to respective NIVO+IPI and sunitinib datasets Justification Combination of best statistical fit and prior clinical input, after re-running survival analyses with the 30-month DBL. See #3 for explanation of why we prefer not to align with committee and ERG preferences for model selection.
6	Utility regression model	30-month DBL data used.	30-month DBL data used.

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
		Justification Data availability; see Part 1.1. A regression model using utility values derived from the EQ-5D-3L data collected in CheckMate 214, with treatment arm, treatment status and progression status included as explanatory variables. Justification ACD 3.14: "*The company's preferred model assumed that people would have different utility values depending on their treatment arm and whether they were on treatment or not. The ERG considered that utility values would also depend on whether the disease had progressed. The committee considered it likely that disease progression would worsen quality of life and concluded progression-status should also be included in the regression model*."	Justification Data availability; see Part 1.1. A regression model using utility values derived from the EQ-5D-3L data collected in CheckMate 214, with treatment arm, treatment status and progression status included as explanatory variables; specifically, Model 7 in Table 1. Justification Table 1's Model 7 is the best fitting model from the stepwise selection process followed, and aligns with the committee's stated preferences for analyses of these data.
7	Subsequent treatment	Subsequent treatment proportions as per CheckMate 214. Justification ACD 3.15: "*The committee concluded that, because all the analyses included the clinical benefits of the subsequent treatments in CheckMate 214, it preferred also to include the costs of those treatments.*"	Subsequent treatment proportions as per CheckMate 214. Justification Alignment with committee preferences.
8	Oral treatment administration	Administration costs applied for sunitinib and pazopanib Justification	Administration costs applied for sunitinib and pazopanib Justification Alignment with committee preferences.

#	Assumption category	Stated or interpreted Committee preference	January 2019 Company preference
		ACD 3.17: "*The ERG….included administration costs for treatment with sunitinib or pazopanib…The committee considered other changes* [including this] *to be reasonable*"	
9	Dosing approach for nivolumab maintenance	Dosing of nivolumab following the first four doses of NIVO+IPI amended to 480mg Q4W, with the first dose given 6 weeks after the last dose of nivolumab plus ipilimumab as per the draft SmPC. This dosing approach amendment also applied to second-line nivolumab monotherapy. Justification Though not considered as part of ACD deliberations, considered likely to be clinical practice if recommended, as described in the opening letter of this document, and therefore appropriate for decision making, at the committee's discretion.	Dosing of nivolumab following the first four doses of NIVO+IPI amended to 480mg Q4W, with the first dose given 6 weeks after the last dose of nivolumab plus ipilimumab as per the draft SmPC. This dosing approach amendment also applied to second-line nivolumab monotherapy. Justification Use of 480mg Q4W flat dosing will not only provide a significant benefit for patients by minimising the number of infusions, but also reducing nurse time and use of NHS resources to provide these infusions by half. It is expected that all patients treated with NIVO+IPI will be treated according to this new dosing schedule.

Key: ACD, appraisal committee document; CS, company submission; DBL, database lock; ERG, Evidence Review Group; EQ-5D-3L, EQ-5D 3-level questionnaire; IO, immuno-oncology; IRRC, independent radiology review committee; KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TTD, time to discontinuation.

1.3. Updated cost-effectiveness model and results

Table 4 and Table 5 show our interpretation of the updated committee and company base case, respectively; each as described in Table 3. While these results are deterministic, and as acknowledged, uncertain projections, both perspectives suggest that NIVO+IPI is a cost-effective option for NHS England patients with advanced, untreated RCC. In interpreting these results, we consider Section 3.22 of the ACD, where the committee note "*that in the company's economic model, people who are considered 'cured' because of an immunologic effect, do not receive a corresponding benefit to health-related quality of life compared to people whose disease had not yet progressed*" and that as a result "*The benefit of any immunological effect may not be fully captured in the QALY calculation*". With this in mind, the case for the committee to revise their ACD conclusions and recommend NIVO+IPI in this indication is compelling.

Table 4: January 2019 Committee-preferred deterministic base case cost-effectiveness results, based on stated and perceived committee preferences from Table 3

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
NIVO+IPI	[redacted]	[redacted]	[redacted]				
Sunitinib	[redacted]	[redacted]	[redacted]	£39,911	1.38	2.65	£28,971
Pazopanib	[redacted]	[redacted]	[redacted]	£38,109	1.38	2.65	£27,663
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab with ipilimumab; QALY, quality-adjusted life years.							

Table 5: Updated company base case pairwise incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
NIVO+IPI	[redacted]	[redacted]	[redacted]				
Sunitinib	[redacted]	[redacted]	[redacted]	£38,838	3.51	1.64	£23,729
Pazopanib	[redacted]	[redacted]	[redacted]	£36,913	3.51	1.64	£22,552
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab with ipilimumab; QALY, quality-adjusted life years.							

2. Additional perceived misrepresentations and inaccuracies

As expressed in our opening letter, we found the ACD to be clear. We also found the ACD to be accurate, with only minor, but sometimes important, exceptions to this finding. Beyond what is stated in Part 1, we are minded to cite to only two sections of ACD text here.

First, Section 3.10. The ACD states, "*The company considered in its base case that, because of the immunomodulatory mechanisms of nivolumab, a proportion of people who have nivolumab would return to a mortality rate equal to that of the general population. This assumes that some people who have nivolumab with ipilimumab are effectively 'cured'. Specifically, the company assumed that half of people who get a 'durable' response seen in the latest CheckMate 214 data-cut would return to the general population mortality rate.*" With reference to Table 3, assumption category #1, this is incorrect. In a cohort-level model, we assume an uncertain probability of an immunomodulatory survival effect. Though in application, the difference may not seem important, conceptually, in the minds of decision-makers, we feel that the distinction is important.

Second, Section 3.21 of the ACD concludes that NIVO+IPI does not meet end-of-life criteria, considering "*that it would be inappropriate to apply special discretion at this time because survival data from CheckMate 214 are immature and there is uncertainty whether the life expectancy of people who would take nivolumab with ipilimumab in UK clinical practice differs from the source of the estimates*". We respect the right of the committee to apply discretion where the committee consider it reasonable, but struggle to reconcile the cited rationale with the decisions another committee (Committee C) applied to end-of-life weights in the recent appraisals of two chimeric antigen receptor T-cell therapies with highly immature survival data and highly limited, non-randomised comparator data (NICE ID1115 and NICE ID1166).

3. References

1. McDermott DF, Rini BI, Motzer RJ, et al. Treatment-Free Survival Following Discontinuation of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma: CheckMate 214 Analysis. European Society for Medical Oncology 2018 Congress. Munich, Germany. 19-23 October 2018. 874P.
2. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Company additional evidence submission 2018. (Updated: 17 December 2018). Accessed: 17 December 2018.
3. European Medicines Agency. OPDIVO: Procedural steps taken and scientific information after the authorisation. 2018. Available at: https://www.ema.europa.eu/documents/procedural-steps-after/opdivo-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed: 2 January 2018.
4. Bristol-Myers Squibb Pharmaceutical Limited. Summary of Product Characteristics. OPDIVO 10 mg/mL concentrate for solution for infusion. 2018.
5. Bristol Myers Squibb. Clinical Protocol CA209214: A Phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma. 13 November 2018. Data on file.
6. Bristol-Myers Squibb. NHS oncologist nivolumab + ipilimumab in renal cell carcinoma model validation meeting report. December 2017. Data on file.
7. National Institute for Health and Care Excellence (NICE). TA417: Nivolumab for previously treated advanced renal cell carcinoma: Final Appraisal Determination: Committee papers. 2017. (Updated: 21 October 2016) Available at: https://www.nice.org.uk/guidance/ta417/documents/committee-papers-2. Accessed: 21 November 2017.
8. National Institute for Health and Care Excellence (NICE). TA483: Nivolumab for previously treated squamous non-small-cell lung cancer: Appraisal committee papers 2. 2017. (Updated: 1 November 2017) Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-5. Accessed: 3 January 2018.
9. National Institute for Health and Care Excellence (NICE). TA484: Nivolumab for previously treated non-squamous non-small-cell lung cancer: Appraisal Committee papers 3. 2017. (Updated: 01 November 2017) Available at: https://www.nice.org.uk/guidance/ta484/documents/committee-papers-6. Accessed: 10 January 2019.
10. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Committee papers. 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10189/documents/committee-papers. Accessed: 10 January 2019.

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Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID1182]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Cancer Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Sharon Deveson Kell

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Nivolumab plus ipilimumab is the first immunotherapy combination proven to be a clinically effective and well-tolerated treatment for untreated advanced renal cell carcinoma (RCC), and has been granted priority review status by the US Food and Drug Administration (FDA). The combination was approved for use by the FDA in April 2018 and is heralded as a breakthrough treatment for untreated advanced RCC. The European Association of Urology (EAU) guidelines have been updated to recommend the use of the nivolumab plus ipilimumab combination as a frontline standard of care for intermediate- and poor-risk patients with untreated advanced RCC.
2	The nivolumab plus ipilimumab combination is well tolerated, and has proven to be more effective at extending progression-free survival and improving overall response rates in intermediate- and poor-risk patients compared to standard first-line treatment with sunitinib. Adding the nivolumab plus ipilimumab combination as a choice in the first-line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life. The improved tolerability of the nivolumab plus ipilimumab combination enhances quality of life and enables patients to contribute socially and economically to society.
3	The committee's decision not to recommend first-line nivolumab plus ipilimumab was based upon the fact that the combination did not meet the end-of-life criteria for a combined population of intermediate- and poor-risk patients, and it is uncertain whether the survival benefit would be maintained in the long-term. However, this model is based upon data from clinical trials, which do not necessarily reflect routine clinical practice. Kidney Cancer Support Network (KCSN) urge NICE to consider funding for the combination through the Cancer Drugs Fund (CDF) to enable collection of real world survival data for intermediate- and poor-risk patients, which could potentially impact the final recommendation.
4	We are disappointed that this innovative and clinically effective treatment for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer): Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families.
5	The nivolumab plus ipilimumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC; however, further efficacy data are required to determine the use of the combination for this cohort of patients. KCSN urge NICE to reconsider the combination for the CDF while further survival data are collected from the cohort of patients with non-clear cell RCC to provide evidence to support this unmet need.
6	The committee's decision to not recommend the nivolumab plus ipilimumab combination for untreated advanced intermediate- or poor-risk RCC patients denies terminally ill kidney cancer patients access to innovative and effective treatment within NHS England, despite the drug being available for kidney cancer patients living in the US and other European countries. This is confusing for the patient community because the committee has acknowledged the fact that the combination is effective, but recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those directly affected by their decision.
7	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made

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	available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.
8	In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and without the nivolumab plus ipilimumab combination, the clinician's choice of treatment is seriously compromised in the first-line. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.
9	Refusal of the nivolumab plus ipilimumab combination will force clinicians to prescribe a less effective first-line treatment for intermediate- and poor-risk advanced RCC, such as a tyrosine kinase inhibitor, which both they and their patients know has a poor side-effect profile and could negatively impact quality of life. In the worst-case scenarios, patients could be left without active treatment to face a premature death.
10	Current first-line treatment options are not effective for everyone. Unjustifiable restrictions in accessing the nivolumab plus ipilimumab combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
11	Nivolumab plus ipilimumab clinical trials have been conducted in untreated advanced RCC patients in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of first-line nivolumab plus ipilimumab on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.
12	Now that the European Medicines Agency (EMA) has approved the nivolumab plus ipilimumab combination, the treatment is available to patients who have private health insurance or who can afford a private prescription, thus creating two-tier access for patients. The NICE appraisal process, therefore, disadvantages less affluent patients, who rely on NHS England to care for them in the later stages of their lives.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We believe the committee has failed to take into account relevant clinical evidence and has not come to a reasonable summary of the clinical effectiveness of this immunotherapy combination. The practice changing impact of ipilimumab + nivolumab in RCC reflects the induction of durable benefit with immunotherapy. Our experts were surprised that the ERG came to the conclusion that there was no evidence of durable benefit. This is untenable and ignores the following evidence: • Nivolumab single agent as a second and subsequent line of therapy in RCC has been approved by NICE following acceptance of evidence of durability of benefit. McDermott et al (Abstract 4507, ASCO 2016) demonstrated a plateau in survival curve due the immunological effect beyond 4 years in pooled data from phase I and II studies. • The phase 1 Checkmate 016 study (Hammers et al Journal of Clinical Oncology 35, (34) 2017 3851-3858) treated 3 cohorts of RCC patients including 47 patients with the ipilimumab 1mg/kg + nivolumab 3mg/kg schedule that was used in the Checkmate 214 registration study. Half of these patients had received previous therapy and would therefore not be expected to do as well as untreated patients. The PFS curve starts to plateau at 2 years and the median follow-up was 22.2 months. This study was updated by Plimack et al at the EIKCS meeting in 2017 with 37.7 month median follow-up (poster submitted to you by BMS). The updated PFS curves show durability beyond 2 years with a marked plateau beyond 3 years. Checkmate 016 was not adequately discussed in the ERG submission and no attempt was made to include the updated data which is in the public domain. • The Checkmate 214 data has been updated with 30 month follow up and we understand has been submitted to the committee. This data confirms durability of PFS with a robust plateau on the Kaplan Meier curve for PFS.
Section 3.1	**'There were currently no data available to estimate the expected proportion of people this would apply to (cure)'.** This is inaccurate because of the data described above. It is entirely reasonable, indeed conservative, to assume that 15% of patients will be cured when treated with first line ipilimumab + nivolumab.
Section 3.2	**'The ERG considered that the immunological effect should be removed entirely because there was no supporting evidence'.** Our experts are concerned about this summary of the ERG analysis and are concerned that the committee has been misled by an ERG appraisal that entirely ignores a) Nivolumab durability of benefit in second line treatment of metastatic RCC b) Mode of action of ipilimumab + nivolumab c) Updated Checkmate 016 data d) Durability of benefit with less active immunotherapies in RCC (IL-2 and IFN) For an ERG to come to the conclusion that no patients would experience durable benefit with immunotherapy betrays a lack of understanding of both the disease and the data. NICE should be able to have confidence in the quality of an ERG assessment. Unfortunately, this assessment falls well short of the standards one would expect. The ERG proposed that the investigator response

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	assessment be used in preference to independent central review because their view was that in clinical practice it would be investigators making assessments of response. This surprising suggestion is at odds with accepted standards of trial design. The ERG's statement that Checkmate 016 'does not include any data on relevant comparators' is inaccurate. A phase I study would not be expected to have a standard arm comparator. The value of Checkmate 016 is as an older dataset with longer follow up which demonstrates durability of benefit in RCC patients treated with ipilimumab and nivolumab.
Section 3.21	**'The committee agreed that, for the combined poor- and intermediate-risk group, there was no robust evidence that average life expectancy was less than 24 months'.** Heng et al, Lancet Oncology 2013 demonstrated that the median OS of patients in the intermediate risk group was 22.5 months and 7.5 months in the poor risk group. Median OS for patients in the intermediate and poor prognostic groups in the Checkmate 214 study who were randomised to receive sunitinib was 18 months. There is no doubt that the outcome for patients with intermediate and poor prognosis RCC satisfies criteria for end-of life treatment. We do not understand why the committee and ERG have stated otherwise and assume this is an error in data interpretation.
Section 3.3	There is no mention of the fact that although TKIs are a current standard of care for intermediate and poor prognosis RCC, they do not result in durable disease control for the vast majority of patients. TKIs are given with relatively short term palliative intent. Combination immunotherapy is given with the intent of gaining long term disease control.
Section 3.7	**'Results uncertain because data immature with a median follow-up of 25.2 months, and only 32.9% of people having nivolumab with ipilimumab had died'.** This would appear to be irrelevant as the committee had already concluded that PFS was the appropriate primary endpoint measure. As an expert body of medical oncologists with specialist experience in the treatment of RCC we believe that ipilimumab + nivolumab is practice changing and is a new standard of care for the first line treatment of metastatic intermediate and poor risk RCC. This combination will confer durable benefit for at least 15% of the treated population. We urge the committee to reverse the ACD decision and to approve ipilimumab + nivolumab for the indicated metastatic RCC population.

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

Name	[redacted]
Role	Pharmaceutical Industry
Other role	[redacted]
Organisation	Ipsen
Location	England
Conflict	
Notes	
Comments on individual sections the ACD:	
) We note from the Committee papers that NHS England have proposed a probable treatment pathway following the introduction of nivolumab+ipilimumab in intermediate-/poor-risk patients. It is not clear whether this proposal is to make nivolumab+ipilimumab the only available treatment in 1st line for intermediate-/poor-risk patients, or an available treatment. It remains the case that some patients will be contraindicated for immunotherapy or will not wish to take it. It is, therefore, important that the other NICE-approved, cost-effective first-line treatments remain available.	

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	RCP, ACP, Bladder and Renal Cancer NCRI Clinical Studies Group
Location	England
Conflict	I contributed patients to this clinical trial and am a co-author on the forthcoming 30 month follow up publication of Checkmate 214 and a quality of life manuscript recently submitted.
Notes	
Comments on the ACD:	
"I write on behalf of the NCRI Renal and Bladder Cancer CSG, the RCP, ACP and the leading Renal Carcinoma Oncology Specialists listed to appeal against this ACD. We believe the committee has failed to take into account relevant clinical evidence and has not come to a reasonable summary of the clinical effectiveness of this immunotherapy combination. The practice changing impact of ipilimumab + nivolumab in RCC reflects the induction of durable benefit with immunotherapy. Remarkably, the ERG came to the conclusion that there was no evidence of durable benefit. This is simply untenable and ignores the following evidence: 1. Nivolumab single agent as a second and subsequent line of therapy in RCC has been approved by NICE following acceptance of evidence of durability of benefit. McDermott et al (Abstract 4507, ASCO 2016) demonstrated a plateau in survival curve due the immunological effect beyond 4 years in pooled data from phase I and II studies. " 2. The phase 1 Checkmate 016 study (Hammers et al Journal of Clinical Oncology 35, (34) 2017 3851-3858) treated 3 cohorts of RCC patients including 47 patients with the ipilimumab 1mg/kg + nivolumab 3mg/kg schedule that was used in	

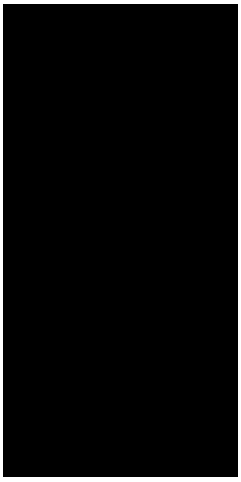
the Checkmate 214 registration study. Half of these patients had received previous therapy and would therefore not be expected to do as well as untreated patients. The PFS curve starts to plateau at 2 years and the median follow-up was 22.2 months. This study was updated by Plimack et al at the EIKCS meeting in 2017 with 37.7 month median follow-up (poster submitted to you by BMS). The updated PFS curves show durability beyond 2 years with a marked plateau beyond 3 years. Checkmate 016 was not adequately discussed in the ERG submission and no attempt was made to include the updated data which is in the public domain."

3. The Checkmate 214 data has been updated with 30 month follow up and we understand has been submitted to the committee. This data confirms durability of PFS with a robust plateau on the Kaplan Meier curve for PFS."
"The ACD summary of evidence and ERG report have the following flaws:

Section 3.1 There were currently no data available to estimate the expected proportion of people this would apply to (cure) . This is inaccurate because of the data described above. It is entirely reasonable, indeed conservative, to assume that 15% of patients will be cured when treated with first line ipilimumab + nivolumab.
"
"Section 3.2 The ERG considered that the immunological effect should be removed entirely because there was no supporting evidence . This is a remarkable summary of the ERG analysis and betrays the unfortunate reality that the committee has been misled by an ERG appraisal that entirely ignores
a) Nivolumab durability of benefit in second line treatment of metastatic RCC
b) Mode of action of ipilimumab + nivolumab
c) Updated Checkmate 016 data
d) Durability of benefit with less active immunotherapies in RCC (IL-2 and IFN)

For an ERG to come to the conclusion that no patients would experience durable benefit with immunotherapy betrays a lack of understanding of both the disease and the data. NICE should be able to have confidence in the quality of an ERG assessment. Unfortunately, this assessment falls well short of the standards one would expect. The ERG proposed that the investigator response assessment be used in preference to independent central review because their view was that in clinical practice it would be investigators making assessments of response. This surprising suggestion is at odds with accepted standards of trial design. The ERG™s statement that Checkmate 016 does not include any data on relevant comparators entirely misses the point. A phase I study would not be expected to have a standard arm comparator. The value of Checkmate 016 is as an older dataset with longer follow up which demonstrates durability of benefit in RCC patients treated with ipilimumab and nivolumab.
"
Section 3.21 ˜™The committee agreed that, for the combined poor- and intermediate-risk group, there was no robust evidence that average life expectancy was less than 24 months™™. Heng et al, Lancet Oncology 2013 demonstrated that the median OS of patients in the intermediate risk group was 22.5 months and 7.5 months in the poor risk group. Median OS for patients in the intermediate and poor prognostic groups in the Checkmate 214 study who were randomised to receive sunitinib was 18 months. There is no doubt that the outcome for patients with intermediate and poor prognosis RCC satisfies criteria for end-of life treatment. We do not understand why the committee and ERG have stated otherwise and assume this is an error in data interpretation.
Section 3.3: There is no mention of the fact that although TKIs are a current standard of care for intermediate and poor prognosis RCC, they do not result in durable disease control for the vast majority of patients. TKIs are given with

relatively short term palliative intent. Combination immunotherapy is given with the intent of gaining long term disease control.
Section 3.7 states the results uncertain because data immature with a median follow-up of 25.2 months, and only 32.9% of people having nivolumab with ipilimumab had died . This would appear to be irrelevant as the committee had already concluded that PFS was the appropriate primary endpoint measure.
As an expert body of medical oncologists with specialist experience in the treatment of RCC we believe that ipilimumab + nivolumab is practice changing and is a new standard of care for the first line treatment of metastatic intermediate and poor risk RCC. This combination will confer durable benefit for at least 15% of the treated population. We urge the committee to reverse the ACD decision and to approve ipilimumab + nivolumab for the indicated metastatic RCC population.
"



"

Company additional evidence submission: Alternative PFS analysis

In the 'Company additional evidence submission' document, provided on 17th December 2018, the company used the [redacted]

In order to provide the committee with cost-effectiveness analysis using a more appropriate measure of PFS, this document repeats the analysis provided on 17th December 2018, using the IRRC measure of PFS (secondary definition) from the August 2017 DBL, and the investigator-assessed (INV) measure of PFS (secondary definition) from the August 2018 DBL. The results remain stable, despite the PFS definition used as presented in Table 1.

Table 1: Company and committee base case ICERs, using alternative PFS measures

PFS measure	Company base case ICER with 2 year stopping rule	Company base case ICER with 5 year stopping rule	Committee base case ICER
[redacted]	£15,800	£23,729	£28,971
18-month IRRC	£14,807	£22,626	£28,921
30-month INV	£13,202	£20,869	£28,856
Key: ICER, incremental cost-effectiveness ratio; INV, investigator assessed; IRRC, independent radiology review committee; PFS, progression free survival			

1. Company base case analysis

New survival analysis was conducted for the two different PFS measures. In both cases (INV Aug-18 and IRRC Aug-17), the choice of survival model for extrapolation of PFS was changed to reflect the best statistical fit, according to AIC and BIC:

- INV Aug-18: Spline 2 knots - odds
- IRRC Aug-17: Spline 2 knots - hazard

With a 2-year stopping rule, the company base case incremental cost-effectiveness ratio (ICER) versus sunitinib using the INV Aug-18 PFS data is £13,202 per QALY gained (Inc. costs - £22,220; Inc. QALYs - 1.68) and using the IRRC Aug-17 PFS data is £14,807 (Inc. costs - £24,390; Inc. QALYs - 1.65).

With a 5-year stopping rule, the company base case incremental cost-effectiveness ratio (ICER) versus sunitinib using the INV Aug-18 PFS data is £20,869 per QALY gained (Inc. costs - £35,422; Inc. QALYs - 1.70) and using the IRRC Aug-17 PFS data is £22,626 (Inc. costs - £37,592; Inc. QALYs - 1.66).

As conducted previously, scenarios considering treatment waning effects and probabilities of an IO effect are presented in Table 2, Table 3, Table 4, and Table 5, for 2-year and 5-year stopping rules, using INV Aug-18 PFS and IRRC Aug-17 PFS, respectively. As sunitinib has lower costs and a higher ICER than pazopanib, only the results for NIVO+IPI versus sunitinib have been shown.

Table 2: Company base case scenarios, using INV Aug-18 PFS, with 2-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	22,220	21,957	21,430	20,931
	Inc QALYs	1.68	1.63	1.52	1.42
	ICER	**13,202**	**13,494**	**14,115**	**14,778**
40% probability of long-term IO effect for durable responders	Inc costs	21,998	21,678	21,065	20,522
	Inc QALYs	1.64	1.57	1.44	1.33
	ICER	**13,441**	**13,826**	**14,621**	**15,436**
30% probability of long-term IO effect for durable responders	Inc costs	21,777	21,400	20,701	20,115
	Inc QALYs	1.59	1.51	1.36	1.24
	ICER	**13,694**	**14,185**	**15,190**	**16,194**
20% probability of long-term IO effect for durable responders	Inc costs	21,557	21,124	20,343	19,716
	Inc QALYs	1.54	1.45	1.28	1.15
	ICER	**13,963**	**14,576**	**15,832**	**17,075**
10% probability of long-term IO effect for durable responders	Inc costs	21,338	20,850	19,991	19,326
	Inc QALYs	1.50	1.39	1.21	1.07
	ICER	**14,249**	**15,007**	**16,569**	**18,119**
0% probability of long-term IO effect for durable responders	Inc costs	21,118	20,580	19,650	18,956
	Inc QALYs	1.45	1.33	1.13	0.98
	ICER	**14,557**	**15,482**	**17,424**	**19,381**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 3: Company base case scenarios, using INV Aug-18 PFS, with 5-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	35,422	35,306	35,011	34,802
	Inc QALYs	1.70	1.67	1.61	1.57
	ICER	**20,869**	**21,112**	**21,737**	**22,205**
40% probability of long-term IO effect for durable responders	Inc costs	35,200	35,055	34,703	34,455
	Inc QALYs	1.65	1.62	1.55	1.49
	ICER	**21,321**	**21,649**	**22,458**	**23,066**
30% probability of long-term IO effect for durable responders	Inc costs	34,979	34,805	34,397	34,110
	Inc QALYs	1.60	1.57	1.48	1.42
	ICER	**21,800**	**22,223**	**23,244**	**24,021**
20% probability of long-term IO effect for durable responders	Inc costs	34,759	34,556	34,094	33,770
	Inc QALYs	1.56	1.51	1.41	1.35
	ICER	**22,308**	**22,841**	**24,107**	**25,086**
10% probability of long-term IO effect for durable responders	Inc costs	34,539	34,308	33,794	33,434
	Inc QALYs	1.51	1.46	1.35	1.27
	ICER	**22,848**	**23,510**	**25,065**	**26,290**
0% probability of long-term IO effect for durable responders	Inc costs	34,320	34,062	33,500	33,107
	Inc QALYs	1.46	1.41	1.28	1.20
	ICER	**23,427**	**24,234**	**26,130**	**27,657**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 4: Company base case scenarios, using IRRC Aug-17 PFS, with 2-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	24,390	24,112	23,570	23,062
	Inc QALYs	1.65	1.59	1.48	1.38
	ICER	**14,807**	**15,150**	**15,895**	**16,701**
40% probability of long-term IO effect for durable responders	Inc costs	24,159	23,817	23,184	22,630
	Inc QALYs	1.60	1.53	1.41	1.29
	ICER	**15,090**	**15,542**	**16,495**	**17,485**
30% probability of long-term IO effect for durable responders	Inc costs	23,929	23,523	22,798	22,196
	Inc QALYs	1.55	1.47	1.33	1.21
	ICER	**15,391**	**15,964**	**17,166**	**18,385**
20% probability of long-term IO effect for durable responders	Inc costs	23,698	23,228	22,411	21,762
	Inc QALYs	1.51	1.41	1.25	1.12
	ICER	**15,709**	**16,423**	**17,921**	**19,425**
10% probability of long-term IO effect for durable responders	Inc costs	23,467	22,931	22,022	21,327
	Inc QALYs	1.46	1.35	1.17	1.03
	ICER	**16,049**	**16,925**	**18,780**	**20,646**
0% probability of long-term IO effect for durable responders	Inc costs	23,235	22,634	21,633	20,890
	Inc QALYs	1.42	1.30	1.09	0.95
	ICER	**16,413**	**17,474**	**19,764**	**22,095**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 5: Company base case scenarios, using IRRC Aug-17 PFS, with 5-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	37,592	37,467	37,161	36,945
	Inc QALYs	1.66	1.64	1.58	1.53
	ICER	**22,626**	**22,894**	**23,593**	**24,118**
40% probability of long-term IO effect for durable responders	Inc costs	37,361	37,204	36,836	36,579
	Inc QALYs	1.62	1.58	1.51	1.46
	ICER	**23,131**	**23,492**	**24,395**	**25,079**
30% probability of long-term IO effect for durable responders	Inc costs	37,130	36,940	36,511	36,213
	Inc QALYs	1.57	1.53	1.44	1.39
	ICER	**23,665**	**24,130**	**25,270**	**26,145**
20% probability of long-term IO effect for durable responders	Inc costs	36,900	36,676	36,186	35,846
	Inc QALYs	1.52	1.48	1.38	1.31
	ICER	**24,232**	**24,817**	**26,228**	**27,329**
10% probability of long-term IO effect for durable responders	Inc costs	36,669	36,409	35,858	35,478
	Inc QALYs	1.48	1.42	1.31	1.24
	ICER	**24,835**	**25,560**	**27,289**	**28,664**
0% probability of long-term IO effect for durable responders	Inc costs	36,436	36,143	35,530	35,109
	Inc QALYs	1.43	1.37	1.25	1.16
	ICER	**25,482**	**26,361**	**28,463**	**30,169**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

2. Committee base case analysis

The assumptions behind the KM plus exponential PFS extrapolation method used for the committee base case were amended to reflect the different PFS measures:

- INV Aug-18: Use KM data from 12 to 30 months for exponential extrapolation, applying the extrapolation from 30 months onwards
- IRRC Aug-17: Use KM data from 8 months to 22 months for NIVO+IPI and 21 months for sunitinib, as per the ERGs assumptions

The committee base case ICER versus sunitinib (using all other assumptions from Table 3 of the Company ACD Response) using the INV Aug-18 PFS data is £28,856 per QALY gained (Inc. costs - £39,516; Inc. QALYs - 1.37) and using the IRRC Aug-17 PFS data is £28,921 (Inc. costs - £39,757; Inc. QALYs - 1.37).

The same treatment stopping rules with treatment waning effect scenarios presented for the company analysis are presented for the preferred committee analysis in Table 6-Table 9.

Table 6: Committee base case scenarios, using INV Aug-18 PFS, with 2-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	22,102	22,441	22,129	21,641
	Inc QALYs	1.67	1.73	1.67	1.57
	ICER	**13,264**	**12,941**	**13,238**	**13,751**
40% probability of long-term IO effect for durable responders	Inc costs	21,471	21,811	21,380	20,840
	Inc QALYs	1.54	1.61	1.52	1.41
	ICER	**13,943**	**13,564**	**14,050**	**14,744**
30% probability of long-term IO effect for durable responders	Inc costs	20,835	21,130	20,579	19,998
	Inc QALYs	1.41	1.47	1.36	1.24
	ICER	**14,748**	**14,357**	**15,117**	**16,065**
20% probability of long-term IO effect for durable responders	Inc costs	20,198	20,381	19,725	19,115
	Inc QALYs	1.29	1.32	1.19	1.07
	ICER	**15,717**	**15,419**	**16,572**	**17,900**
10% probability of long-term IO effect for durable responders	Inc costs	19,557	19,544	18,817	18,189
	Inc QALYs	1.16	1.15	1.01	0.88
	ICER	**16,906**	**16,934**	**18,659**	**20,615**
0% probability of long-term IO effect for durable responders	Inc costs	18,913	18,583	17,851	17,217
	Inc QALYs	1.03	0.96	0.81	0.69
	ICER	**18,401**	**19,324**	**21,909**	**25,051**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 7: Committee base case scenarios, using INV Aug-18 PFS, with 5-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	36,910	37,054	37,376	37,132
	Inc QALYs	1.68	1.71	1.78	1.73
	ICER	**21,943**	**21,657**	**21,053**	**21,506**
40% probability of long-term IO effect for durable responders	Inc costs	36,279	36,454	36,686	36,402
	Inc QALYs	1.56	1.59	1.64	1.58
	ICER	**23,319**	**22,915**	**22,407**	**23,034**
30% probability of long-term IO effect for durable responders	Inc costs	35,644	35,831	35,928	35,613
	Inc QALYs	1.43	1.47	1.49	1.42
	ICER	**24,950**	**24,439**	**24,185**	**25,037**
20% probability of long-term IO effect for durable responders	Inc costs	35,006	35,171	35,097	34,764
	Inc QALYs	1.30	1.33	1.32	1.25
	ICER	**26,908**	**26,365**	**26,606**	**27,758**
10% probability of long-term IO effect for durable responders	Inc costs	34,365	34,443	34,188	33,854
	Inc QALYs	1.17	1.19	1.14	1.07
	ICER	**29,306**	**28,986**	**30,066**	**31,634**
0% probability of long-term IO effect for durable responders	Inc costs	33,721	33,558	33,192	32,879
	Inc QALYs	1.04	1.01	0.94	0.87
	ICER	**32,311**	**33,196**	**35,400**	**37,584**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 8: Committee base case scenarios, using IRRC Aug-17 PFS, with 2-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	22,343	22,682	22,370	21,881
	Inc QALYs	1.67	1.74	1.68	1.58
	ICER	**13,368**	**13,041**	**13,341**	**13,858**
40% probability of long-term IO effect for durable responders	Inc costs	21,711	22,052	21,621	21,081
	Inc QALYs	1.55	1.61	1.53	1.42
	ICER	**14,052**	**13,670**	**14,160**	**14,859**
30% probability of long-term IO effect for durable responders	Inc costs	21,076	21,371	20,820	20,239
	Inc QALYs	1.42	1.48	1.37	1.25
	ICER	**14,864**	**14,470**	**15,235**	**16,189**
20% probability of long-term IO effect for durable responders	Inc costs	20,439	20,622	19,966	19,356
	Inc QALYs	1.29	1.33	1.20	1.07
	ICER	**15,839**	**15,540**	**16,700**	**18,035**
10% probability of long-term IO effect for durable responders	Inc costs	19,798	19,784	19,058	18,430
	Inc QALYs	1.16	1.16	1.01	0.89
	ICER	**17,036**	**17,064**	**18,797**	**20,758**
0% probability of long-term IO effect for durable responders	Inc costs	19,154	18,823	18,092	17,458
	Inc QALYs	1.03	0.97	0.82	0.69
	ICER	**18,539**	**19,465**	**22,053**	**25,191**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

Table 9: Committee base case scenarios, using IRRC Aug-17 PFS, with 5-year treatment stopping rule

Scenario		Treatment waning effect (time from treatment stopping rule)			
		None	**10 years**	**5 years**	**3 years**
50% probability of long-term IO effect for durable responders	Inc costs	37,151	37,295	37,616	37,373
	Inc QALYs	1.69	1.72	1.78	1.73
	ICER	**22,019**	**21,732**	**21,128**	**21,582**
40% probability of long-term IO effect for durable responders	Inc costs	36,520	36,695	36,927	36,642
	Inc QALYs	1.56	1.60	1.64	1.59
	ICER	**23,396**	**22,992**	**22,483**	**23,111**
30% probability of long-term IO effect for durable responders	Inc costs	35,885	36,072	36,169	35,854
	Inc QALYs	1.43	1.47	1.49	1.43
	ICER	**25,027**	**24,517**	**24,262**	**25,114**
20% probability of long-term IO effect for durable responders	Inc costs	35,247	35,412	35,337	35,004
	Inc QALYs	1.31	1.34	1.32	1.26
	ICER	**26,984**	**26,442**	**26,683**	**27,833**
10% probability of long-term IO effect for durable responders	Inc costs	34,606	34,684	34,428	34,095
	Inc QALYs	1.18	1.19	1.14	1.08
	ICER	**29,378**	**29,059**	**30,137**	**31,699**
0% probability of long-term IO effect for durable responders	Inc costs	33,962	33,798	33,433	33,120
	Inc QALYs	1.05	1.02	0.94	0.88
	ICER	**32,375**	**33,256**	**35,450**	**37,621**

Key: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; NA, not applicable; QALY, quality-adjusted life year.

ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID 1182]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/36/11

Completed 18th January 2019

CONFIDENTIAL DATA REDACTED

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

NIVOLUMAB IN COMBINATION WITH IPILIMUMAB FOR UNTREATED ADVANCED OR METASTATIC RENAL CELL CARCINOMA [ID1182]

1. ERG critique of company response to the ACD

The Evidence Review Group (ERG) received the company's submitted response to the appraisal consultation document (ACD) on 14 January 2019 for the appraisal of nivolumab in combination with ipilimumab (NIVO+IPI) for untreated advanced or metastatic renal cell carcinoma (RCC). The company then submitted further evidence and an updated model on 16 January 2019. The company's response included cost-effectiveness results from a revised model. The company revised its original model using a combination of the committee's preferred assumptions as stated in the ACD, new assumptions that were not discussed in the first Appraisal Committee (AC) meeting, and new analyses based on an updated data cut (30 months, August 2018) from the CheckMate 214 trial. This document presents a critique of the nine revisions identified by the company in Table 3 of its response to the ACD.

1.1 Immunotherapeutic effect

The AC concluded after the first AC meeting that the probability of an immunotherapeutic (IO) effect was highly uncertain, and that it could lie anywhere between the company's optimistic [50%] and ERG's conservative [0%] assumptions. The company has interpreted the AC's conclusion to mean that the AC's preferred assumption is that durable responders will experience an IO effect with a probability of 25%. The ERG disputes this interpretation of the ACD and instead understands it to indicate that the AC considers that using a plausible range is an appropriate approach for decision making. The ERG maintains its preference for an assumption of 0% probability of an IO effect as it does not consider the company's expectation that a long-term survival benefit following treatment with NIVO+IPI equates to a cure for advanced RCC to be supported by evidence. The ERG does not consider the ICERs per QALY gained generated by the company scenario analyses investigating the effect of varying the proportion of patients experiencing an IO effect to be meaningful, as the implementation of the IO effect in the model is flawed.

Meaning of long-term survival benefit

Clinical opinion suggests that a long-term survival benefit might be expected in some patients due to treatment with immunotherapy. The company has assumed that this means that a proportion of patients can be cured of advanced RCC (represented by general mortality rates in the model). The ERG has not seen any evidence to suggest that a long-term survival benefit following treatment with immunotherapy effectively equates to a cure for advanced RCC. The

company references clinical opinion that patients with a durable response would be likely to receive a long-term survival benefit; however, the report referenced by the company[1] does not specify the expectation that a proportion of patients with a durable response would return to a general mortality rate (as is the case in the company model). The ERG analysed the available survival data from a variety of trials[2-9] for patients treated with nivolumab or ipilimumab for advanced RCC or advanced melanoma in its original report (Section 5.4.3). The ERG did not find any evidence to suggest that patients in the included trials[2-9] were subject to general mortality rates at the time of the data cut reported in the published papers.

Modelling of long-term survival benefit

Even if it were considered plausible that a proportion of patients would be cured of advanced RCC by treatment with NIVO+IPI, it is not possible to investigate the impact of varying the proportion of patients cured in the company model. This is because the company's modelling of the IO effect is flawed (as noted in Section 5.4.3 of the original ERG report).

The company has used a mixed model to incorporate a probability that a proportion of patients treated with NIVO+IPI would experience a return to general mortality. This has been achieved by modelling overall survival (OS) for two cohorts: one that does not experience an IO effect and one that does (Figure 1). The cohort that does not experience an IO effect follows a log-normal distribution in the company revised base case. The cohort that experiences an IO effect follows the same log-normal distribution as the cohort without an IO effect until OS reaches 30% (which occurs at around 9 years), after which general mortality rates are applied. General mortality rates are applied when OS reaches 30% to represent the proportion of patients who had a durable response to treatment in the CheckMate 214 trial. Modelled OS for the two cohorts are then combined at a ratio of 50:50 in the company's revised base case and 75:25 in the company's interpretation of the AC's preferred assumption.

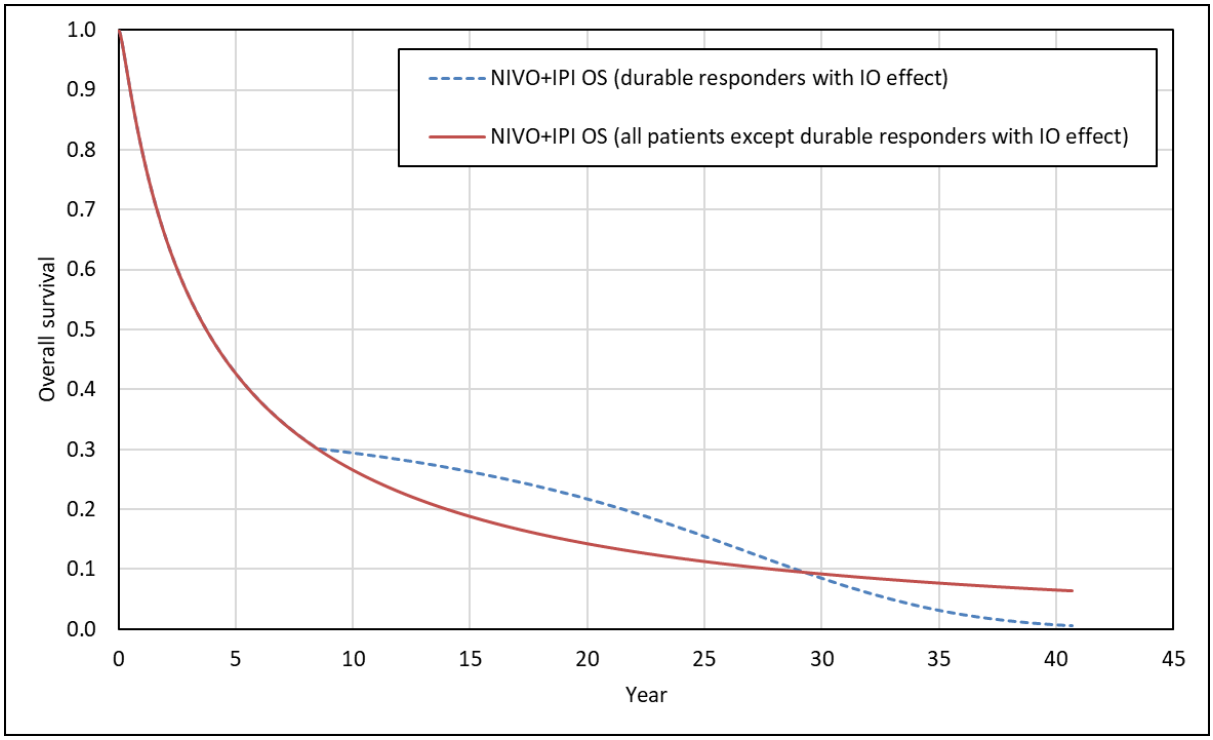


Figure 1 Company modelling of OS for patients with and without an immunological effect

This approach to modelling implies that:

a) The proportion of patients who have a durable response to treatment with NIVO+IPI is linked to the time at which general mortality rates are applied. It is not linked to the proportion of patients who have a durable response. In the company base case, patients who experience an IO effect do so suddenly 9 years after beginning treatment; the probability of survival of this group until this point is equal to probability of survival of the rest of the population. Figure 2 shows how the time at which general mortality rates are applied changes depending on the proportion of patients estimated to experience a durable response; for instance, general mortality rates are applied after 9 years when 30% of patients have a durable response but general mortality rates are applied after 14 years when 20% of patients have a durable response. These implications are unjustified by the company and the ERG considers them to be implausible.

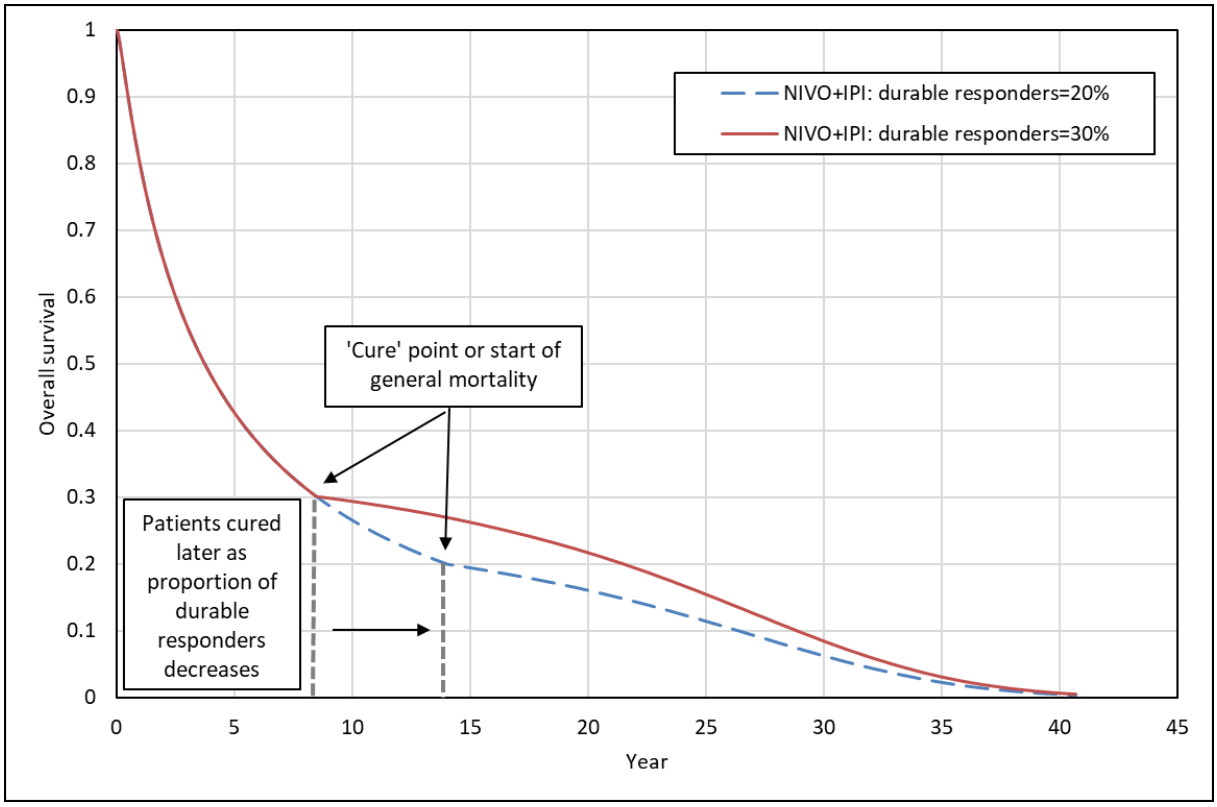


Figure 2 Effect of proportion of durable responders on start point of general mortality rates

b) The only patients still alive at 9 years and beyond are patients who achieved a durable response, whether or not they experienced an IO effect. This can be observed if the model is set to 100% probability of an IO response (99% in practice due to the particulars of the coding). In theory, this should set the model so that all patients with a durable response experience an IO effect but, crucially, should not affect OS for the 70% of patients who do not achieve a durable response. However, setting the model to 100% probability of an IO effect results in all patients returning to general mortality rates at 9 years. This means that modelled OS includes OS for durable responders only and implies that all patients without a durable response have died. Again, this assumption is unjustified by the company and the ERG considers it to be implausible.

The ERG would have preferred to see OS for durable responders (with and without IO effect) modelled separately from the non-durable responder cohort in order to avoid these implausible outcomes.

Link to progression-free survival

Durable response is defined in the original company submission as "patients who initially responded to treatment and were still responding at the latest available follow-up" (CS, p. 32), which clearly links the notion of durable response with progression-free survival (PFS) as

patients who are responding will not yet have progressed. The concept of durable response is also linked with OS in the company model, as only patients with a durable response are modelled to experience an IO effect, an effect that cures them of advanced RCC. Thus, PFS and OS are theoretically linked in the company model via the concept of durable response; however, this link is not modelled. That is to say that changing the proportion of patients modelled to experience an IO effect on OS does not impact on PFS. It is possible, therefore, that some patients who experience an IO effect and are effectively cured of the disease are also modelled to experience progression. The ERG has not been able to investigate this potential issue thoroughly in the time available, but highlights it as an area of uncertainty.

Proportion of patients with a durable response

The ERG notes that the company has not updated the proportion of patients exhibiting a durable response following the 30-month data cut. The company's base case ICER per QALY gained is negatively associated with the proportion of durable responders, so any decrease in the estimate of the proportion of durable responders will result in an increase in the ICER per QALY gained.

1.2 Stopping rule

The original company base case included a stopping rule after 5 years. It was noted in the ACD that the company had not explored the effect of the stopping rule on clinical outcomes nor had it been presented with evidence to support the assumption that a stopping rule would not have an effect on clinical outcomes. The AC considered it inappropriate to include a stopping rule without evidence of its effect on clinical outcomes. However, the company has included a 5-year stopping rule in its updated base case (14 January model).

The company states that it has confidence in the continued benefit of NIVO+IPI beyond the end of treatment and does not consider that stopping treatment after either 2 or 5 years would have any effect on clinical outcomes (LY or QALYs gained). It does not present any clinical evidence to support this assertion; however, it notes that [redacted].

The company instead presents scenario analyses to investigate the effect on the ICER per QALY gained of a treatment waning effect on OS following discontinuation of treatment. The company notes that treatment waning effects are included in a similar manner to those in previous NICE technology appraisals for nivolumab,[10,11] but it is not clear from the published documentation exactly how these effects were incorporated previously. The treatment waning effect is incorporated in the revised company model by setting cycle hazard rates for treatment with NIVO+IPI to equal those for treatment with sunitinib after a given number of months from

beginning treatment. The treatment waning effect is applied only to those patients who do not experience an IO effect.

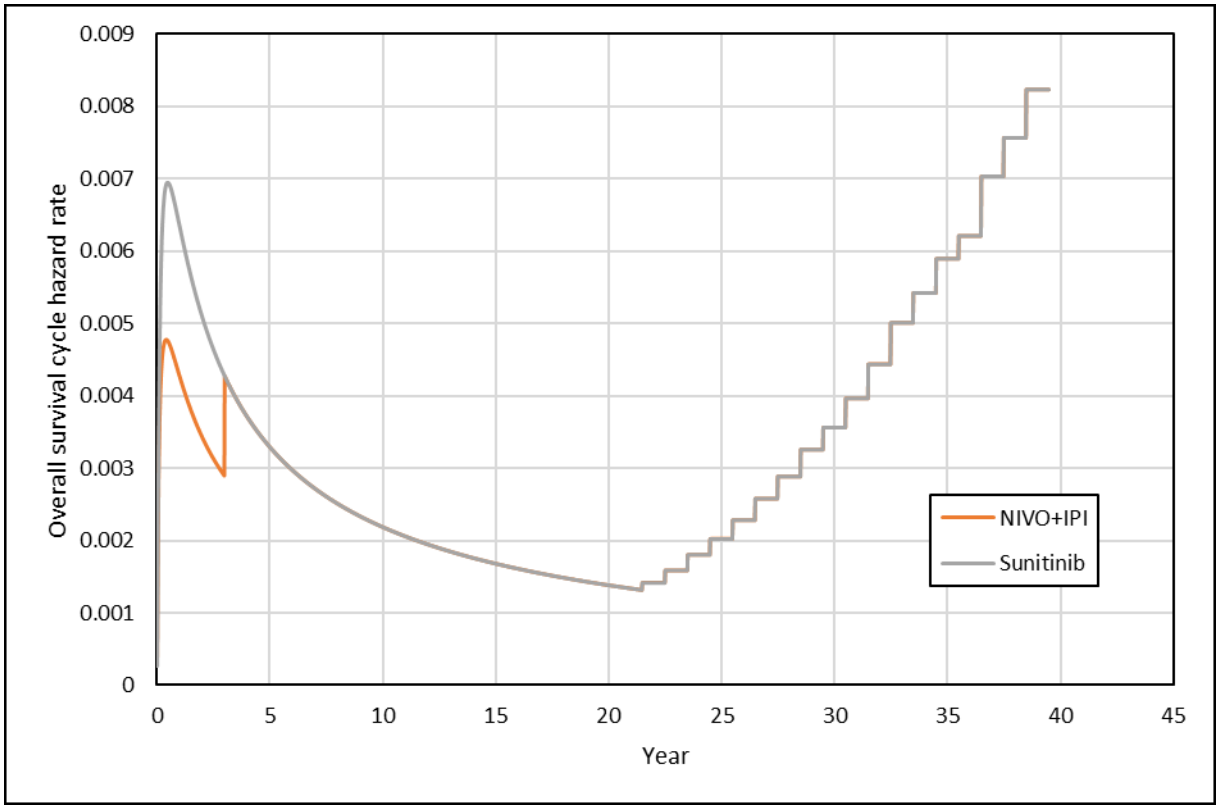


Figure 3 Overall survival cycle hazard rates for 3-year treatment waning effect in company revised model

The ERG has two principal concerns about the way a treatment waning effect is implemented in the model:

a) The immediate jump in cycle hazard rates for patients treated with NIVO+IPI (Figure 3) is clinically implausible. A more gradual increase in hazard rates for treatment with NIVO+IPI would result in a lower benefit attributable to treatment with NIVO+IPI and lower OS than is modelled in the company treatment waning scenarios.

b) There does not appear to be a link between the treatment stopping rule and treatment waning effect. The treatment waning effect is calculated from the beginning of treatment regardless of the length of the stopping rule applied.

The ERG's preferred approach is not to include a stopping rule due to concerns related to the way the treatment waning effect is considered in scenario analyses and the lack of evidence to support the company's assertion that there would be no effect on clinical outcomes of discontinuing treatment before progression.

The ERG notes that the company has not included any quality of life benefit due to the application of a stopping rule. The company notes that NHS England[12] considers clinicians' acceptance of stopping rules to reflect increasing concerns about the longer term toxicities of immunotherapy. This would imply that there may be some quality of life benefit to stopping treatment before progression.

1.3 Time to treatment discontinuation

The company has amended the modelling of time to treatment discontinuation (TTD) data so that TTD for treatment with sunitinib and treatment with pazopanib are equal in accordance with the AC's preference, and it has updated its modelling to include new evidence from the 30-month data cut from the CheckMate 214 trial.

[redacted]. The ERG is satisfied that the updated company modelling of TTD data from the CheckMate 214 trial is appropriate.

1.4 Progression-free survival

After the first meeting, the AC preferred the independent radiology review committee (IRRC)-assessed secondary-definition of PFS from the CheckMate 214 trial for use in the model. It also preferred the use of a K-M plus exponential curve approach to estimate PFS beyond the end of the trial. The secondary definition of PFS was defined in the CheckMate 214 trial as the time from the beginning of the trial until progression or death (which is the more usual definition of PFS seen in clinical trials) and so included data on patients who received subsequent treatment before their disease progressed. The primary definition of PFS was defined as the time until subsequent treatment, progression or death, which the ERG noted in its original report introduced the potential for informative censoring in the results.

[redacted] The company submitted further evidence using the investigator (INV)-assessed secondary-definition of PFS from the 30-month data cut alongside the IRRC-assessed secondary-definition PFS (18-month data cut) model from its original submission.

The impact on the ICER per QALY gained of choosing either INV-assessed or IRRC-assessed PFS data is around £2,000 when the company's preferred spline models are used to model the data, with the IRRC-assessed data generating higher ICERs per QALY gained than the

INV-assessed data. There is almost no impact on the ICER per QALY gained of using INV-assessed or IRRC-assessed PFS data when K-M plus exponential models are used to model the data (Table 1). The ERG has chosen the IRRC-assessed data (secondary definition) modelled using the K-M plus exponential approach for its preferred base case, as this represents the most conservative estimate out of the company's preferred method and the AC's preferred method after the first meeting.

Table 1 ICERs per QALY gained when using various PFS models

	K-M data plus exponential		Spline	
	INV-assessed 30-month data cut	**IRRC-assessed 18-month data cut**	**INV-assessed 30-month data cut**	**IRRC-assessed 18-month data cut**
Company base case	£23,786	£23,876	£20,868	£22,626
Company interpretation of AC base case	£28,856	£28,921	£25,600	£27,368

Source: Company models 14 January 2019 (PFSINVS Aug 18 and PFSIRCS Aug 17)

1.5 Overall survival

Patients treated with sunitinib were allowed to crossover onto NIVO+IPI when the trial was stopped early following analysis of the results from the 18-month data. It is not clear from the evidence submitted by the company how it has dealt with the issue of crossover in the 30-month data cut.

The company has fitted independent log-normal models to the OS data from the updated 30-month data cut from the CheckMate 214 trial. These log-normal models represent survival for all patients who are not modelled to experience an IO effect and return to general mortality following treatment with NIVO+IPI (first- or second-line treatment), which is 70% of patients in the company base case. The ERG has two principal concerns with the company's modelling of OS for patients who do not experience an IO effect. First, patients who do not experience an IO effect are modelled to have a lower mortality rate than patients who do experience an IO effect (and are essentially cured of RCC) after 20 years (Figure 4). The ERG considers it to be clinically implausible that patients who are cured of advanced RCC should have a greater risk of death than those who are not considered to be cured. The company did not provide any justification for this outcome of the model.

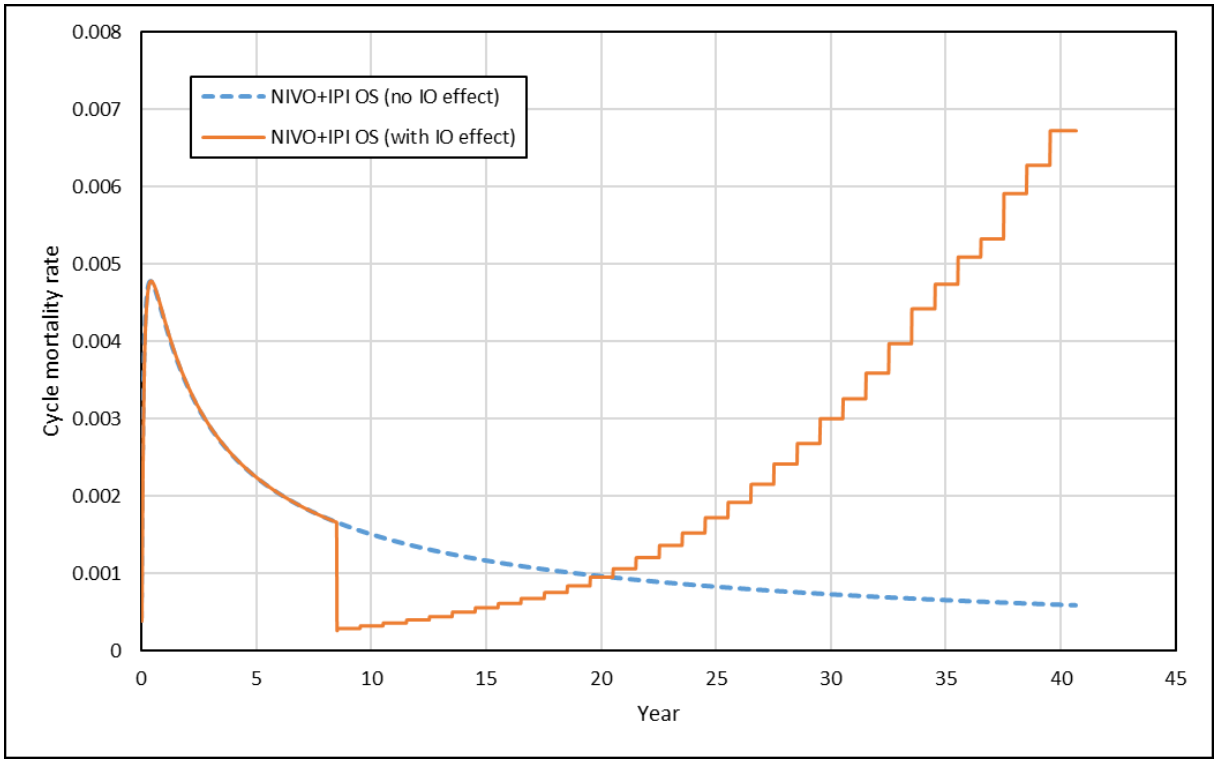


Figure 4 NIVO+IPI mortality rates: company log-normal model with and without immunological effect

Source: Company model 14 January 2019

Second, the ERG considers the log-normal model to be inappropriate for modelling long-term survival. This is because the log-normal model exhibits continuously decreasing mortality rates after the early portion of the curve, which can lead to biologically implausible results. In the company model, the log-normal models used by the company predict that 9.4% of patients with advanced RCC who are treated with NIVO+IPI but who do not benefit from an IO effect will still be alive at the age of 90, 30 years after beginning treatment (Table 2). The company model also predicts that 3.8% of patients with advanced RCC who are treated with sunitinib or pazopanib will still be alive at the age of 90. Using UK mortality rate data from the Office for National Statistics[13] adjusted to match the proportion of males and females in the company model, 2.6% of the sex-adjusted UK population who were 60 years old in 2017 would be expected to reach 90 years old. This means that the company log-normal models predict that a substantially greater proportion of people who are treated for advanced RCC and do not experience an IO effect will live to at least 90 years old than in the general population of the UK. The ERG does not consider this to be a plausible outcome.

The ERG has not remodelled the OS data from the 30-month data cut given the time available for this critique. The ERG's preferred approach to extrapolating the OS data remains the K-M

plus exponential piecewise model, based on the models presented by the company in its response to the ACD. Nonetheless, the ERG considers that the K-M plus exponential approach generates more plausible results than the log-normal model, as it predicts that 0.3% of patients treated with NIVO+IPI will still be alive at an age of 90 years (versus 2.6% in the general population). The ERG considers that the K-M plus exponential approach still generates optimistic results, as it also results in mortality rates for patients with advanced RCC who are treated with NIVO+IPI that are higher than general mortality rates 33 years after beginning treatment.

Table 2 Comparison of company log-normal and K-M plus exponential OS models with general UK population

	ONS	NIVO+IPI		Sunitinib	
		Log-normal	K-M+ exponential	Log-normal	K-M+ exponential
Proportion of 60 year olds alive at 90	2.6%*	9.4%	0.3%	3.8%	0%
Time when mortality rates exceed general mortality	-	20 years	33 years	22 years	39 years

Source: Company model; ERG calculations; ONS life tables

* Assuming 2017 annual mortality rates for each age category

The ERG notes that the exponential portion of the company's piecewise model for treatment with sunitinib is fitted to the data from 7 to 30 months rather than the full data set in order to take account of the effect of censoring and crossover in the latter part of the data (Figure 5). The ERG does not consider this to be a methodologically robust approach to dealing with crossover and would have liked to have seen an exploration of adjustment methods for treatment crossover.

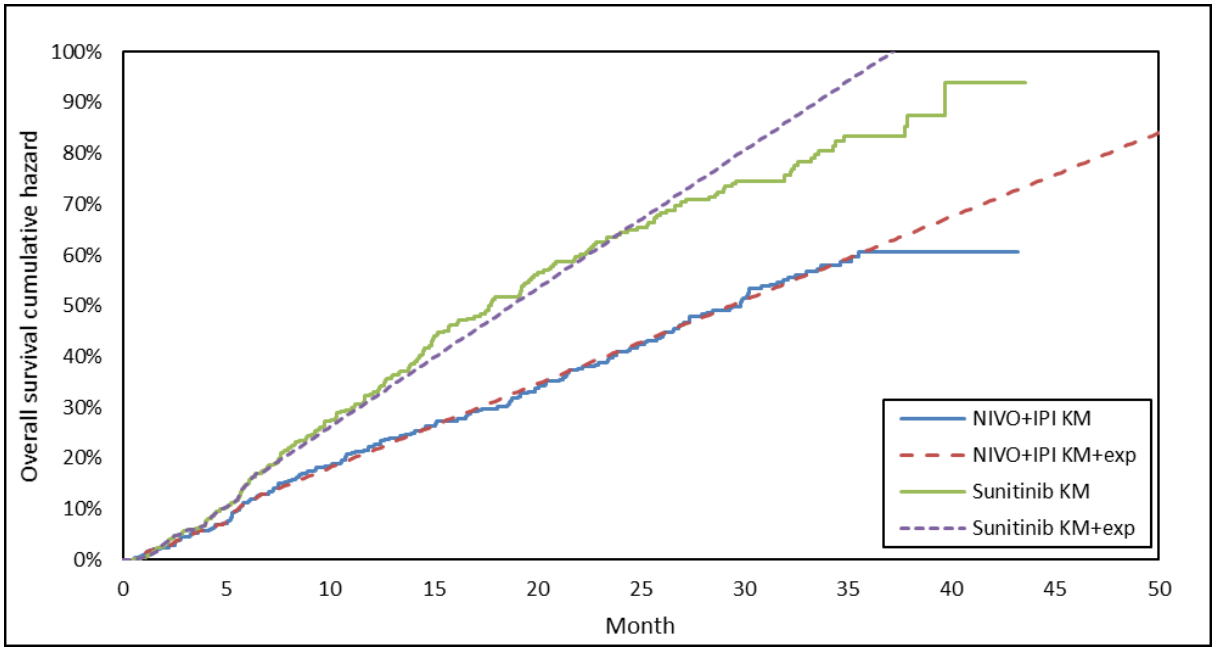


Figure 5 Company piecewise OS model cumulative hazard plot

Source: Company model 14 January 2019

1.6 Utility values

The company previously estimated health state utility values for the economic model using a regression-based analysis of the CheckMate 214 trial data (18-month data cut). The final model chosen by the company in that analysis showed that health state utility values depend on treatment status and treatment arm, but not on disease progression status. The analysis has now been updated using the latest data cut from the CheckMate 214 trial (30-month data cut). The final utility model in the updated analysis shows that health state utility values depend on (i) disease progression status, (ii) treatment status and (iii) treatment arm.

The ERG notes that for individuals who are on first-line treatment, the utility value for the post-progression (PP) health state is higher than for the progression-free (PF) health state (Table 3).

Table 3 Health state utility value estimated by the company from the CheckMate 214 trial data, by treatment arm (30-month data cut)

	NIVO+IPI	Sunitinib
PF on treatment utility	0.793	0.754
PF off treatment utility	0.749	0.707
PP on treatment utility	0.794	0.763
PP off treatment utility	0.702	0.707

PF=progression-free; PP=post-progression
Source: Company model 14 January 2019

The ERG considers that this anomaly may be due to a correlation between treatment status and disease progression, since patients who experience disease progression are likely to have already discontinued first-line treatment. Median PFS is greater than median TTD in the CheckMate 214 trial, which means that, on average, patients discontinued first-line treatment before progression. Median PFS (IRRC-assessed secondary definition) was 11.2 months and median TTD was 7.4 months for treatment with NIVO+IPI. Median PFS (IRRC-assessed secondary definition) was 8.5 months and median TTD was 6.0 months for treatment with sunitinib.

The ERG reiterates the point from its original critique of the company submission that the company only considered seven utility models out of the possible eight, from which the final utility model was chosen on the basis of Akaike information criterion (AIC) and Bayesian information criterion (BIC). The eighth utility model, which would have estimated health state utility values based on treatment arm and disease progression status, has not been considered. Even if the eighth utility model had a poorer fit to the CheckMate 214 trial data (according to AIC and BIC) than the final utility model, the health state utility values would likely have been more clinically plausible since the correlation issue would not be present.

As the company has not presented information about the eighth model, the ERG has investigated the effect of applying the same health state utility value for patients on treatment (0.793 for NIVO+IPI and 0.763 for sunitinib and pazopanib) to PF and PP. Changing the PP on treatment utility value to equal the PF on treatment utility value has no impact on the ICER per QALY gained, as no patients are modelled to enter in the PP on treatment state in the company base case.

1.7 Subsequent treatment

The ERG is satisfied that this change has been implemented correctly in the model.

1.8 Treatment administration costs

The ERG is satisfied that this change has been implemented correctly in the model.

1.9 Dosing approach for nivolumab maintenance

The ERG is satisfied that this change has been implemented correctly in the model. The ERG notes that the flat dosing regimen used in the company's updated model is different to the weight-based dosing regimen used in the CheckMate 214 trial. The company has assumed that clinical outcomes using a flat dosing regimen will be the same as for weight-based dosing and has not amended any clinical outcomes in the model to incorporate a dosing effect. As well as implementing a flat-dosing regimen, the company has assumed that all patients will

receive infusions on a 4-weekly rather than 2-weekly basis (both frequencies are licensed in this indication). This assumption reduces the costs associated with nivolumab maintenance therapy due to the fewer resources required to administer the treatment.

2. Overview of ERG preferred assumptions

The ERG's preferred assumptions regarding the amendments outlined in the company's response to the ACD are shown in Table 4.

Table 4 Overview of ERG preferred assumptions regarding company response to ACD

Issue	Preferred assumption	Justification
1. Immunotherapeutic effect	0%	a) No evidence provided to indicate that an expected long-term survival benefit from treatment with NIVO+IPI equates to a cure for advanced RCC b) Even if treatment with NIVO+IPI does cure a proportion of people with advanced RCC, the implementation is flawed in the model and produces various clinically implausible results that have not been justified.
2. Stopping rule	None	a) No evidence provided on potential impact on clinical outcomes of stopping treatment in patients who are still benefitting b) Flawed implementation of scenario analyses to investigate potential impact of treatment waning effect.
3. Time to treatment discontinuation	Company [redacted] model	[redacted].
4. Progression-free survival	IRRC-assessed secondary definition (18-month data cut) modelled using K-M plus exponential	There is not a lot to choose from between the company's preferred spline models and the K-M plus exponential approach; however, the K-M plus exponential approach is more stable to the underlying data. The IRRC-assessed K-M plus exponential model produces the most conservative ICERs per QALY gained.
5. Overall survival	K-M plus exponential approach	Various clinically implausible results generated by company log-normal model. K-M plus exponential model was preferred by AC after first meeting and appears to have reasonable face validity when applied to updated data cut. ERG notes that sunitinib data have not been adjusted for crossover by any standard methods.
6. Utility values	Using PF on treatment utility values for PP on treatment	Regression model including progression status produces unusual results where patients on treatment after progression have a higher utility value than patients who have not yet progressed. This is likely due to correlation between treatment status and progression status. Company has not presented a full model including all covariates, so effect of correlation cannot be assessed. Adjusting PP on treatment utility to equal PF on treatment utility removes the anomaly.
7. Subsequent treatment	Subsequent treatment proportions as per CheckMate 214	AC preference.
8. Oral treatment administration	Administration costs applied for sunitinib and pazopanib	AC preference.

9. Dosing approach for nivolumab maintenance	As per company implementation	The ERG has not been presented with any evidence to support the equality of clinical outcomes using weight-based and flat dosing regimens for nivolumab maintenance therapy, nor for changing the frequency of infusions from every 2 weeks to every 4 weeks. The ERG highlights that this is an area of uncertainty.

3. Effect on the ICER per QALY gained of the ERG's revisions to the company updated base case

The ERG has carried out the following revisions to the company updated base case ICERs per QALY gained (14 January 2019 model) for treatment with NIVO+IPI versus treatment with sunitinib and versus treatment with pazopanib:

- Remove immunotherapeutic survival effect [R1]
- Remove stopping rule [R4]
- Use IRRC-assessed secondary definition of PFS (18-month data cut) modelled using K-M plus exponential [R10]
- Use K-M plus exponential approach to model OS data (30-month data cut) [R11]
- Use PF on treatment utility value for PP on treatment utility value [R12]

Numbering of revisions continues from ERG's previous model revisions, in line with the format of the updated company model. Details of all Microsoft Excel revisions carried out by the ERG to the company's model are presented in the Appendix of this document (Section 5).

A summary of the individual effects of the ERG's model amendments on the company's updated base case cost effectiveness results for the comparison of treatment with NIVO+IPI and treatment with sunitinib are shown in Table 5. A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with NIVO+IPI and treatment with pazopanib are shown in Table 6.

The cost-effectiveness results in Table 5 and Table 6 use PAS prices for nivolumab, ipilimumab and pazopanib. The results in Table 5 and Table 6 use list prices for all other drugs.

Table 5 Cost effectiveness using PAS prices (NIVO+IPI versus sunitinib): ERG revisions to company base case

Revision	NIVO+IPI			Sunitinib			Incremental			ICER per QALY gained	Change from company base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company updated base case (14 January 2019 model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£38,838***	***1.64***	***3.51***	***£23,729***	
R1) Remove immunotherapeutic survival effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,683	1.41	2.88	£26,813	+£3,084
R4) Remove stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,351	1.64	3.51	£25,817	+£2,088
R10) PFS = IRRC-assessed 2nd definition K-M+exponential model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,025	1.63	3.51	£23,877	+£148
R11) Overall survival = K-M plus exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,352	1.69	3.47	£23,303	-£425
R12) Use PF on treatment utility value for PP on treatment utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,838	1.64	3.51	£23,729	£0
ERG revised base case (R1, R4, R10, R11, R12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£39,699***	***1.05***	***1.81***	***£37,694***	***+£13,966***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; IRRC=independent radiology review committee; K-M=Kaplan-Meier LY=life years; OS=overall survival; PF=progression-free; PFS=progression-free survival; PP=post-progression; QALY=quality adjusted life year

Table 6 Cost effectiveness using PAS prices (NIVO+IPI versus pazopanib): ERG revisions to company base case

Revision	NIVO+IPI			Pazopanib			Incremental			ICER per QALY gained	Change from company base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company updated base case (14 January 2019 model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£36,913***	***1.64***	***3.51***	***£22,552***	
R1) Remove immunotherapeutic survival effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,758	1.41	2.88	£25,443	+£2,891
R4) Remove stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,426	1.64	3.51	£24,643	+£2,091
R10) PFS = IRRC-assessed 2nd definition K-M+exponential model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,100	1.63	3.51	£22,699	+£146
R11) Overall survival = K-M plus exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,427	1.69	3.47	£22,163	-£389
R12) Use PF on treatment utility value for PP on treatment utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,913	1.64	3.51	£22,552	£0
ERG revised base case (R1, R4, R10, R11, R12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£37,774***	***1.05***	***1.81***	***£35,866***	***+£13,314***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; IRRC=independent radiology review committee; K-M=Kaplan-Meier LY=life years; OS=overall survival; PF=progression-free; PFS=progression-free survival; PP=post-progression; QALY=quality adjusted life year

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5. Appendix: Microsoft Excel revisions made by the ERG to the company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*letter* where *letter* = A to K. A menu of revisions and Mod names appears below and on the 'ERG switches' worksheet in the ERG amended model.

These revisions are applicable to the updated model version submitted by the company in response to the ACD on 14 January 2019, filename: **1182 NIVO+IPI ERG v1 14 Jan 2019 [ACIC].xlsb**

Instructions for modifying the updated company model

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F9

1. Paste the following table into sheet 'ERG switches' in cells K4:O15. Name switches Mod_J and Mod_K (all other switches already named)

Revision #	Name	Switch	Description	Instructions
Correction	Mod_A	1	Company correction to ipilimumab treatment cost calculation	Use switch (0,1)
R1	-	-	Remove immunotherapeutic survival effect	Set Controls!F107 to 0%
R2	Mod_B	0	ERG remodelled OS estimates from CheckMate 214	Use switch (0,1)
R3	Mod_C	0	ERG remodelled PFS estimates from CheckMate 214	Use switch (0,1)
R4	-	-	Remove stopping rule	Set Controls!F42 to "No"
R5	Mod_D	0	ERG remodelled TTD estimates from CheckMate 214 (without stopping rule)	Use switch (0,1)
R6	Mod_E	1	Assume pazopanib TTD=sunitinib TTD	Use switch (0,1)
R7	Mod_F	0	Model 7 utility values including all three main effects	Use switch (0,1)
R8	-	-	Use CheckMate 214 proportions for subsequent treatments	Set Controls!F113 to "CheckMate 214"
R9	Mod_H	1	Add administration costs for suntinib and pazopanib	Use switch (0,1)
R10	Mod_J	0	Use IRRC-assessed 2nd def of PFS (18-mth data cut) using K-M+exp	Use switch (0,1) and set Controls!F85 to "KM+exp"
R11	-	-	Use K-M+exp to model OS data (30-month data cut)	Set Controls!F76 to "KM+exp"
R12	Mod_K	0	Use PF on treatment utility for PP on treatment utility	Use switch (0,1)

2. Move sheet from *1182 NIVO+IPI_ERG critique ACD response_additional data.xlsx* into the model

3. Set model to company base case values using button on Controls sheet

4. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R1) Remove immunotherapeutic survival effect	-	Controls	F107	No modification to company model. Set to 0%
R4) Remove stopping rule	-	Controls	F42	No modification to company model. Set to "No"
R6) Assume pazopanib TTD=sunitinib TTD	Mod_E			No modification to company model
R8) Use CheckMate 214 proportions for subsequent treatments	-	Controls	F113	No modification to company model. Set to "CheckMate 214"
R9) Add administration costs for suntinib and pazopanib	Mod_H			No modification to company model

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R10) Use IRRC-assessed 2nd def of PFS (18-mth data cut) using K-M+exp	Mod_J	PFS	AO31: AO2153	=IF(Mod_J=0,'KM+exp'!AU13,'PFS_IRRC_2_KM+exp'!E11)
R10) Use IRRC-assessed 2nd def of PFS (18-mth data cut) using K-M+exp	Mod_J	PFS	BD31: BD2153	=IF(Mod_J=0,'KM+exp'!AY13,'PFS_IRRC_2_KM+exp'!F11)
R10) Use IRRC-assessed 2nd def of PFS (18-mth data cut) using K-M+exp	Mod_J	Controls	F85	Set to “KM+exp”
R11) Use K-M+exp to model OS data (30-month data cut)	-	Controls	F76	No modification to company model. Set to “KM+exp”
R12) Use PF on treatment utility for PP on treatment utility	Mod_K	Utilities	D51	=IF(Mod_K=0,p_u_214.constant+p_u_214.prog.dec,UTILITY_PFSonTx_nivoipi)
R12) Use PF on treatment utility for PP on treatment utility	Mod_K	Utilities	E51	=IF(Mod_K=0,p_u_214.constant+p_u_214.arm.dec+p_u_214.prog.dec+p_u_214.interaction.arm.pro.dec, UTILITY_PFSonTx_sunit)
R12) Use PF on treatment utility for PP on treatment utility	Mod_K	Utilities	F51	=IF(Mod_K=0,IF(cont.utility_pazo="Equal to sunitinib",UTILITY_PPSonTx_sunit,UTILITY_PPSonTx_sunit+0.1*(UTILITY_PPSonTx_nivoipi-UTILITY_PPSonTx_sunit)),UTILITY_PFSonTx_pazo)

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F9

BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID1182: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma

Executive summary

Commercial arrangement: NHS England (NHSE) shall be entitled to an overall discount of [redacted]% (or [redacted]% after value added tax [VAT]-adjustment) on nivolumab for this indication.

Data collection arrangement: The data collection would be anticipated to conclude in either August 2020 or 2021, when it is expected that the 5-year and 6-year follow-up data respectively will be available from the CheckMate 214 trial.

Introduction

This document provides details of the commercial and data collection arrangement being proposed by Bristol Myers Squibb (BMS) as part of this appraisal. This offering is designed to ensure that patients have access to this important new treatment while data are collected which will address the Committee's concerns highlighted in the second Appraisal Committee Meeting (ACM) and subsequent discussions between the National Institute for Health and Care Excellence (NICE), NHSE and BMS.

The feedback from the ACM on the 22nd January is the Committee has uncertainty in the long-term survival of patients on NIVO+IPI which has an impact on the cost-effectiveness of NIVO+IPI. In this proposal we present analyses using different parametric extrapolations along with a commercial scheme to manage the uncertainty.

These analyses result in ICERs for NIVO + IPI versus sunitinib between £20,885 and £26,307 which are all below the £30,000 per quality-adjusted life year (QALY) threshold.

This greatly reduces the risk to NICE and NHSE from approving this indication for use. Furthermore, the provision of 5- or 6- year data for this indication will significantly reduce the uncertainty regarding the long-term efficacy of NIVO+IPI, and provide a unique opportunity to characterise the long-term survival of NIVO+IPI in this indication.

Unmet need in untreated advanced renal cell carcinoma

There remains a significant unmet need for patients who have untreated advanced renal cell carcinoma. Patients with advanced RCC have a life-threatening condition and face a worsening life expectancy with increasing adverse prognostic factors. Standard first-line management in the NHS is currently restricted to systemic VEGFR tyrosine kinase inhibitor agents that have no proven significant benefit on OS, and can be associated with significant toxicity.[1-4] There is a clear unmet need for new treatment modalities to improve physician and patient choice and potentially improve the life expectancy of patients.

NIVO+IPI is the first immunotherapeutic agent licensed for use in first-line advanced RCC and thus represents a 'step-change' in the management of this disease for patients. In intermediate-/poor-risk patients (a population with the highest unmet medical need and most severe prognosis), NIVO+IPI has clearly shown the potential to significantly improve life expectancy and quality of life for those with untreated advanced RCC

Revised commercial arrangement

BMS understand that the Appraisal Committee have concerns about the cost-effectiveness of NIVO+IPI given the potential range of incremental cost-effectiveness ratios (ICERs) resulting from the different OS extrapolation methods used. Given the preference of the Committee to consider ICERs both from analyses using the ERG's more conservative survival modelling approach (Kaplan–Meier [KM] followed by extrapolation of select KM data using the exponential function) and from the company approach (extrapolation using the entirety of the KM data, with a log-normal curve chosen based on the best statistical fit), BMS are willing to offer an increased confidential commercial discount to ensure that the plausible ICERs for NIVO+IPI are below a £30,000 per QALY gained willingness-to-pay threshold. The commercial scheme will be administered directly with NHS England as a confidential rebate on the acquisition of nivolumab as part of NIVO+IPI treatment (induction and maintenance phases) for intermediate-/poor-risk patients with untreated advanced renal cell carcinoma.

In addition to the agreed NHS price reduction of [redacted]% for nivolumab in all indications, NHS England shall be entitled to receive a rebate of [redacted]% on the invoiced spend (equivalent to an overall discount of [redacted]% or [redacted]% after VAT adjustment, **Table** 1) of nivolumab for this indication. The rebate will be based on the number of vials used for untreated advanced RCC in intermediate-/poor-risk patients in addition to the confidential NHS discount price. All rebates will include a VAT 'true-up' – calculation of this amount is provided in Table 1.

Table 1: Calculation of VAT 'true-up' for nivolumab for untreated advanced renal cell carcinoma in intermediate-/poor-risk patients using 4-ml vial

[redacted] xxxx xxxx Xxxx

xxxx

xxxx

[redacted]

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

Revised ICERs

The revised commercial proposal is based on the ERG's preferred economic assumptions, as presented in Tables 5 and 6 of the ERG Addendum, dated 18th January 2019.[5] As the committee consider the OS extrapolation method used by the ERG (KM data plus exponential without any patients reaching general population mortality risk) to be conservative (Appraisal Consultation Document [ACD] 3.10)[6], analyses are presented below using a range of OS extrapolation methods. Cost-effectiveness results using extrapolation with log-normal and log-logistic treatment-independent curves (using the entirety of the CheckMate 214 OS data) are also presented. Log-normal and log-logistic curves both fit the data well according to Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, and meet the expectations of clinicians interviewed for the company submission (5-year OS between 35% and 45% for NIVO+IPI).[7] Log-normal and log-logistic extrapolations have decreasing hazards over time, resulting in approximately 15% of NIVO+IPI patients and 5% and 6% of sunitinib (and pazopanib) patients receiving general population mortality risk (as the model is programmed to ensure probability of death can be no lower than the average for the age-adjusted general-population), respectively.

As preferred by the Committee, the analyses shown do not include any treatment stopping rules or any explicit modelling of long-term immunotherapeutic survival benefit from

response to NIVO+IPI or subsequent nivolumab monotherapy beyond the standard parametric survival model extrapolations limited by general population mortality.

The ICERs using the Committee's preferred economic assumptions for the current patient access scheme (PAS) and the proposed commercial scheme with the revised rebate applied for nivolumab, are presented in Table 2. Results using a log-normal and log-logistic extrapolation for OS are shown in Table 3 and Table 4, respectively.

The results in Table 2 to Table 4 show that when using the proposed Cancer Drug Fund (CDF) commercial scheme, NIVO+IPI is cost-effective across analyses using a range of different OS extrapolations, with all ICERs below £30,000 per QALY gained, even in the absence of any immunotherapeutic survival assumptions for durable responders.

Table 2: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the ERG Addendum, dated 18th January 2019), using KM plus exponential for OS extrapolation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER, NIVO+IPI versus (£/QALY)
Current baseline commission patient access scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£39,699	1.05	£37,694
Pazopanib	[redacted]	[redacted]	£37,774	1.05	£35,866
Proposed CDF commercial scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£27,706	1.05	£26,307
Pazopanib	[redacted]	[redacted]	£25,781	1.05	£24,479

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 3: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the ERG Addendum, dated 18th January 2019), using log-normal for OS extrapolation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER, NIVO+IPI versus (£/QALY)
Current baseline commission patient access scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£41,375	1.41	£29,410
Pazopanib	[redacted]	[redacted]	£39,449	1.41	£28,042
Proposed CDF commercial scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£29,381	1.41	£20,885
Pazopanib	[redacted]	[redacted]	£27,456	1.41	£19,517

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 4: Pairwise cost-effectiveness results using the ERG revisions to the company base case (Table 5 and 6 of the ERG Addendum, dated 18th January 2019), using log-logistic for OS extrapolation

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER, NIVO+IPI versus (£/QALY)
Current baseline commission patient access scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£40,273	1.19	£33,792
Pazopanib	[redacted]	[redacted]	£38,348	1.19	£32,177
Proposed CDF commercial scheme ([redacted]%)					
NIVO+IPI	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	£28,279	1.19	£23,729
Pazopanib	[redacted]	[redacted]	£26,354	1.19	£22,113

Abbreviations: CDF: Cancer Drugs Fund; ERG: Evidence Review Group; KM: Kaplan–Meier; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PAS: patient access scheme.

Data collection proposal

1 Purpose of data collection proposal

The purpose of this data collection proposal is to outline how BMS propose to address the Committee's existing concerns with longer-term data from its existing clinical trial package for NIVO+IPI.

2 Proposed commencement and period of agreement

This proposed data collection arrangement would take effect on publication of the managed access agreement. The data collection would be anticipated to conclude in either August 2020 or 2021, when it is expected that the 5-year and 6-year follow-up data respectively will be available from the CheckMate 214 trial.

3 Anticipated patient eligibility

If NIVO+IPI were recommended for use in the CDF, it is anticipated that key patient eligibility criteria for NIVO+IPI's use in the Cancer Drugs Fund would be aligned to the licensed indication. These will be determined by NHS England in consultation with NICE and BMS.

4 Area(s) of clinical uncertainty

The long-term overall survival was a key area of uncertainty identified by the NICE committee. The primary source of data to address these will be the ongoing trial described under bullet 5 below.

5 Source(s) of data collection

Data collection from the ongoing clinical trial (CheckMate 214) will be the primary source of data collection. A 5-year data cut from the CheckMate 214 trial is expected in August 2020 with a 6-year data expected in August 2021. Table 5 provides a brief description of the trial.

Clinical trial

As per the most recent database lock (6 August 2018), there are [redacted] in follow-up or still on treatment in the CheckMate 214 trial. Based on lognormal or KM plus exponential OS extrapolations from the economic model, we anticipate between [redacted] and [redacted], or [redacted] and [redacted] patients will be in follow up or still on treatment at 5 and 6 years respectively.

Table 5: CheckMate 214 overview

CheckMate 214 – Phase III study (n=1390)
Description: Multicentre, open-label, randomised phase III study, with nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg solutions IV Q3W for 4 doses then nivolumab 3 mg/kg solutions IV Q2W
Primary Endpoint: IRRC-assessed ORR and PFS, and OS, in intermediate-/poor-risk subjects with previously untreated advanced or metastatic RCC
Secondary Endpoints: IRRC-assessed ORR and PFS, and OS, in any-risk subjects with previously untreated RCC. Incidence of AEs in all treated subjects with previously untreated advanced or metastatic RCC
Exploratory Endpoints: Overall safety and tolerability of NIVO+IPI versus sunitinib. IRRC-assessed ORR and PFS, and OS in favourable-risk subjects with previously untreated advanced or metastatic RCC. Explore potential predictive biomarkers of clinical response

by analyzing tumor specimens and blood samples for proteins and genes involved in regulating immune responses. Evaluate HRQoL as assessed by FACT-G. Assess disease related symptoms in each arm based on NCCN FKSI-19. Assess changes in global health status based on EuroQol's EQ-5D.

Abbreviations: AE: adverse event; EQ-5D: EuroQoL 5-Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-19: Functional Assessment of Cancer Therapy-Kidney Symptom Index; HRQoL: health-related quality of life; IRRC: Independent radiological review committee; IV: intravenous; NCCN; National Comprehensive Cancer Network: NIVO+IPI; nivolumab plus ipilimumab; ORR: Overall Response Rate, OS: Overall Survival, PFS: Progression free survival, Q2W: every 2 weeks, Q3W: every 3 weeks, RCC: renal cell carcinoma.

SACT

5.1 The Systemic Anti-Cancer Therapy (SACT) dataset is a mandated dataset as part of the Health and Social Care Information Standards. Data can also be collected via the SACT dataset during the data collection arrangement period, specifically:

- Overall survival
- Duration of therapy

6 Outcome data to be collected

Clinical trial

6.1 The most pertinent outcome to be measured is long-term overall survival. At the end of the data collection period, data will be available from the ongoing CheckMate 214 trial. This will be supplemented by the data collected in SACT.

SACT

6.2 Data collection via SACT will support data collected in the clinical trial. During the managed access agreement period, SACT will collect data on overall survival and duration of treatment.

7 Proposed data analysis plan

7.1 Analyses will be provided for NIVO+IPI for untreated advanced RCC in patients with intermediate-/poor-risk from the ongoing clinical trial and SACT.

References

1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007; 356(2):115-24.
2. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind Phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European Journal of Cancer. 2013; 49(6):1287-96.
3. Schmidinger M. Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. EJC Suppl. 2013; 11(2):172-91.
4. Ravaud A. Treatment-associated adverse event management in the advanced renal cell carcinoma patient treated with targeted therapies. Oncologist. 2011; 16 Suppl 2(Suppl 2):32-44.
5. National Institute for Health and Care Excellence (NICE). ID1182: Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma: Appraisal consultation document. 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10189/documents/appraisal-consultation-document. Accessed: 5 February 2019.
6. Liverpool Reviews and Implementation Group (LRiG). Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID 1182]: Addendum. 18 January 2019. Not yet published.
7. Bristol-Myers Squibb. NHS oncologist nivolumab + ipilimumab in renal cell carcinoma model validation meeting report. December 2017. Data on file.

ERG CRITIQUE: CDF PROPOSAL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID 1182]

Confidential until published

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Completed 14th February 2019

CONFIDENTIAL DATA REDACTED

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

NIVOLUMAB IN COMBINATION WITH IPILIMUMAB FOR UNTREATED ADVANCED OR METASTATIC RENAL CELL CARCINOMA [ID1182]

ERG CRITIQUE OF COMPANY CANCER DRUG FUND (CDF) PROPOSAL

The Evidence Review Group (ERG) received the company's submitted cancer drug fund (CDF) proposal for the recommendation of nivolumab in combination with ipilimumab (NIVO+IPI) for untreated advanced or metastatic renal cell carcinoma (RCC) on 08 February 2019. The company CDF proposal includes (i) a commercial arrangement for treatment with NIVO+IPI and (ii) alternative modelling approaches for overall survival (OS). The company did not submit a revised economic model alongside its CDF proposal. The company has instead used the ERG's modifications to its updated base case (14 January 2019) to examine the impact of alternative modelling approaches for OS.

1. Company cost effectiveness results

Commercial arrangements that offer the NHS discounts off the list price of nivolumab, ipilimumab and pazopanib were included in the company's original base case (06 February 2018) and updated base case (14 January 2019). In the company CDF proposal, the discount on the list price of nivolumab increased to [redacted] while the discount on list price of ipilimumab and pazopanib remained unchanged.

Table 1 and Table 2 summarise the cost effectiveness results in the company CDF proposal using PAS prices for nivolumab, ipilimumab and pazopanib, and list prices for all other drugs.

Table 1 Cost effectiveness results in company CDF proposal using PAS prices (NIVO+IPI versus sunitinib)

Revision	NIVO+IPI			Sunitinib			Incremental			ICER per QALY gained	Change from base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
ERG modification to updated base case (14 January 2019 model) including original PAS discount ([redacted]) ***Overall survival = K-M plus exponential***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£39,699***	***1.05***	***1.81***	***£37,694***	
CDF commercial scheme=[redacted]; Overall survival = K-M plus exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,706	1.05	1.81	£26,307	-£11,388
CDF commercial scheme=[redacted]; Overall survival = Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,381	1.41	2.88	£20,885	-£16,809
CDF commercial scheme=[redacted]; Overall survival = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,279	1.19	2.33	£23,729	-£13,966

CDF=cancer drug fund; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LY=life years; OS=overall survival; QALY=quality adjusted life year
Source=company cancer drug fund proposal, Tables 2, 3 and 4

Table 2 Cost effectiveness results in company CDF proposal using PAS prices (NIVO+IPI versus pazopanib)

Revision	NIVO+IPI			Pazopanib			Incremental			ICER per QALY gained	Change from base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
ERG modification to updated base case (14 January 2019 model) including original PAS discount ([redacted]) ***Overall survival = K-M plus exponential***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£37,774***	***1.05***	***1.81***	***£35,866***	
CDF commercial scheme=[redacted]; Overall survival = K-M plus exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,781	1.05	1.81	£24,479	-£11,388
CDF commercial scheme=[redacted]; Overall survival = Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,456	1.41	2.88	£19,517	-£16,350
CDF commercial scheme=[redacted]; Overall survival = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,354	1.19	2.33	£22,113	-£13,753

CDF=cancer drug fund; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LY=life years; OS=overall survival; QALY=quality adjusted life year
Source=company cancer drug fund proposal, Tables 2, 3 and 4

2. Overview of ERG modifications to the company model accepted by the company

The ERG identified four issues in the updated company base case (14 January 2019) and its modifications to the company model at the second AC meeting. The company had included an immunotherapeutic (IO) effect and a 5-year stopping rule in its original base case (06 February 2018) and updated base case (14 January 2019). The Appraisal Committee (AC) at the first and second AC meeting considered it inappropriate to include either assumption in the base case without any clinical evidence to support the continued benefit of NIVO+IPI beyond the end of treatment. The AC also preferred the use of a piecewise model approach for modelling progression-free survival (PFS) and OS whereby the Kaplan Meier (K-M) data from the Checkmate 214 trial is used as much as possible before appending an exponential tail to the K-M data. The company accepts the four modifications to its updated base case in the CDF proposal. Table 3 summarises changes to the updated company base case following the ERG's critique.

Table 3 Summary of further evidence submitted by the company in response to the second appraisal committee meeting

Issue	Company base case (14 January 2019)	CDF base case (06 February 2019)
1. IO effect	50% probability of IO survival effect for durable responders only. Justification Clinical opinion to the company was that IO effect would occur in those patients who have a durable response, and that these patients would likely experience a long-term survival benefit.	0% probability of IO survival effect for durable responders only. Justification AC preference
2. Stopping rule	5-year stopping rule included for treatment with NIVO+IPI Justification The protocol amendment to the Checkmate 214 trial that [redacted] and prolonged benefit of NIVO+IPI	No stopping rule included for treatment with NIVO+IPI Justification AC preference
3. Progression-free survival	Using the IRRC-assessed secondary definition of progression, independent cubic spline 2-knots hazard curves were fitted to NIVO+IPI and sunitinib K-M data (18-month data cut) Justification Combination of best statistical fit and prior clinical input, after re-running survival analyses with the 30-month data cut	Using the IRRC-assessed secondary definition of progression, exponential curves are appended to NIVO+IPI and sunitinib K-M data (18-month data cut) Justification AC preference
4. Overall survival	Independent log-normal curves were fitted to NIVO+IPI and sunitinib K-M data (30-month data cut) Justification Combination of best statistical fit and prior clinical input, after re-running survival analyses with the 30-month OS data	K-M plus exponential piecewise curves are fitted to NIVO+IPI and sunitinib K-M data (30-month data cut) - the company explored the use of log-normal and logistic curves Justification AC preference plus company's exploratory analyses

AC=appraisal committee; CDF=Cancer Drugs Fund; ERG=evidence review group; IRRC=Independent radiology review committee; IO=immunotherapeutic; K-M=Kaplan Meier; OS=overall survival;

3. ERG comment on the revised commercial arrangement

The ERG is satisfied that this change has been implemented correctly in the model.

4. ERG comments on company additional overall survival analyses

The company states that it has removed any IO effect for the modelling of OS according to the preference of the AC. The company also states that the AC considered the K-M plus exponential curve approach to be conservative at the second AC meeting. The company therefore presents cost effectiveness results using the K-M plus exponential parametric extrapolation of the Checkmate 214 trial data (30 months, August 2018 data cut off) in the

CDF proposal, and also explored the use of log-normal and log-logistic extrapolations best statistical fit and prior clinical advice to the company. The ERG has replicated the parametric analyses for modelling overall survival for treatment with NIVO+IPI and treatment with sunitinib. The ERG is satisfied that changes have been implemented correctly and confirms that it is able to reproduce the cost effectiveness results presented by the company in the CDF proposal. The ERG notes that current log-normal and log-logistic curves still predict that a substantial proportion of patients treated with NIVO+IPI will be cured of advanced RCC (Table 4 and Figure 1). The ERG reiterates its preference for K-M plus exponential as a conservative estimate due to the lack of evidence or justification that patients are cured and/or when patients are cured.

The piecewise K-M plus exponential curve, log-normal curve and log-logistic curve each predict that all patients who live for a certain amount of time after beginning treatment with either NIVO+IPI or sunitinib will be cured. Compared with the K-M plus exponential curve, patients are cured much sooner with the log-normal and log-logistic models. The log-normal and log-logistic curves predict that patients treated with NIVO+IPI who survive for around 19 years will be cured of advanced RCC (Figure 1). At this point, all patients still at risk from the disease have died leaving only the population which has been cured. Similarly, patients treated with sunitinib who survive for around 20 years are modelled to be cured of the disease (Figure 2).

The ERG considers there to be no evidence that there would be no patients still at risk of the disease 19 or 20 years after beginning treatment. With the K-M plus exponential curve, patients treated NIVO+IPI and sunitinib are modelled to be cured after 30 years (Table 4). It is important to bear in mind the patient population under consideration have advanced RCC and have not been modelled to benefit from any IO effect in the first or subsequent line settings. OS estimates from the log-normal and log-logistic curves should therefore be interpreted with caution.

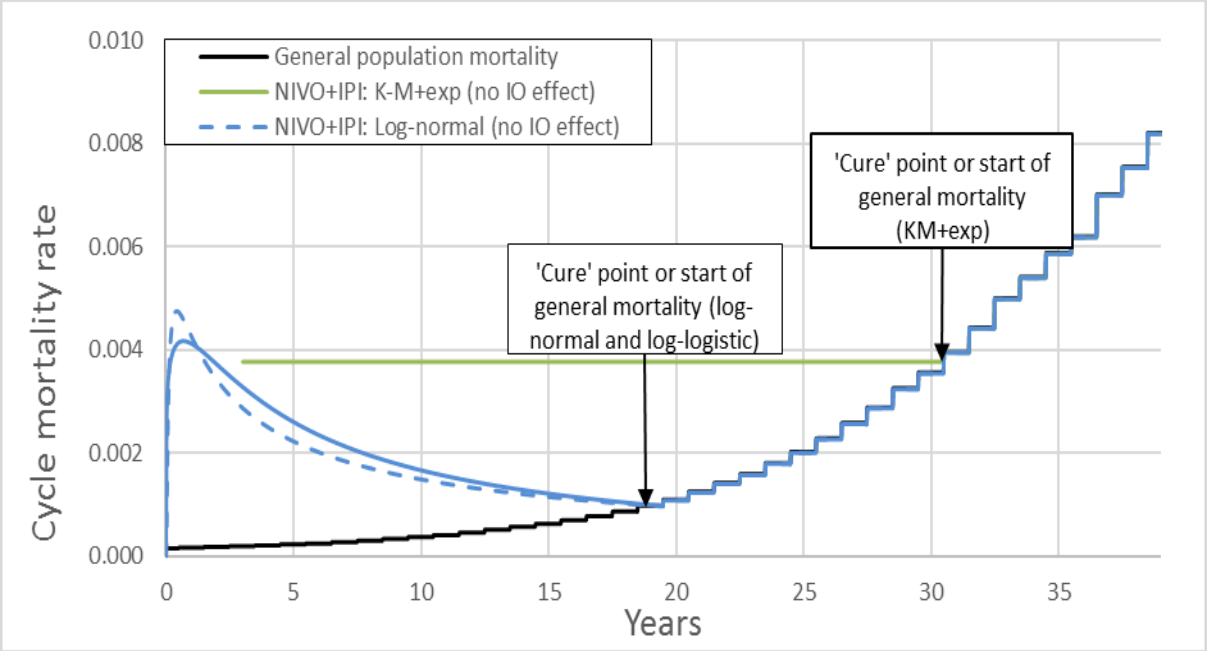

Figure 1 NIVO+IPI mortality rates: company K-M plus exponential (exponential segment), log-normal and log-logistic models, age and sex-match general mortality cap

Source: Company model 14 January 2019

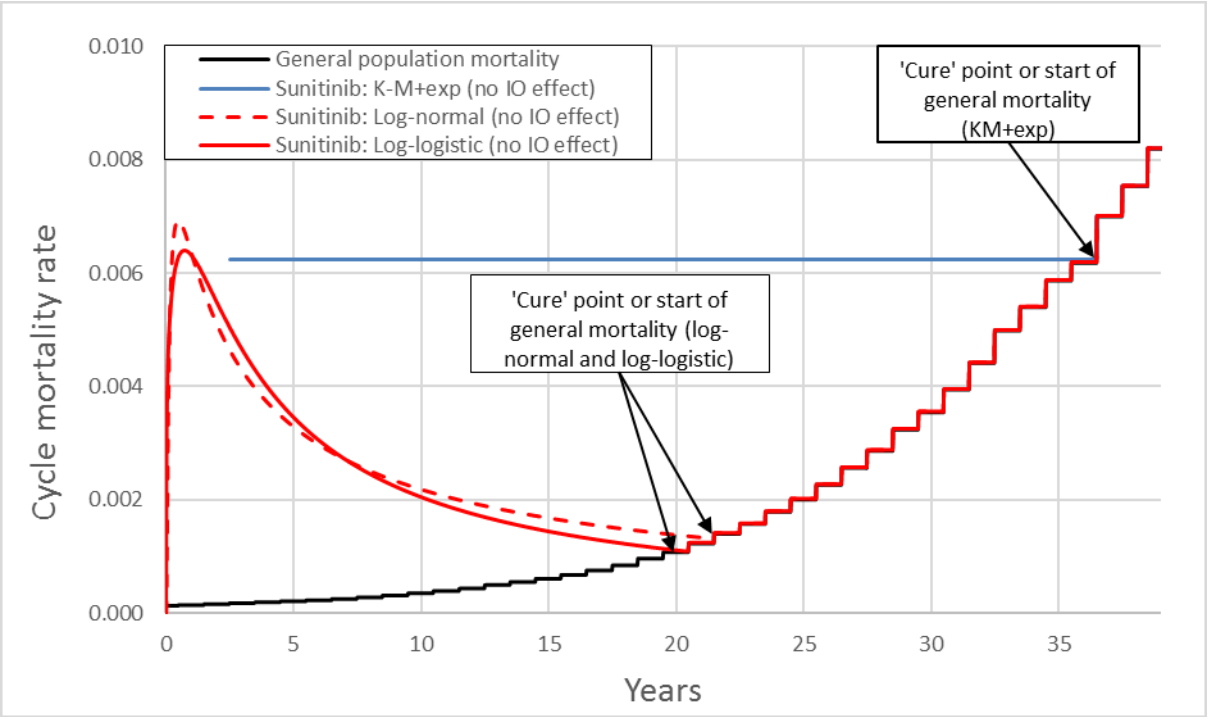

Figure 2 Sunitib mortality rates: company K-M plus exponential (exponential segment), log-normal and log-logistic models, age and sex-match general mortality cap

Source: Company model 14 January 2019

Each of the OS curves presented by the company represent a long term-benefit for a proportion of patients treated with NIVO+IPI; however, the K+M plus exponential curve does not model a cure in the way that the log-logistic and log-normal models do. The incremental life years (LYs) generated by the model are 1.81, 2.88 and 2.33 when K-M plus exponential, log-normal and log-logistic curves were used to estimate OS. Given that there is no clinical evidence to support the existence of a cure with treatment with NIVO+IPI or sunitinib, the ERG considers that the use of K-M plus exponential curve is preferred as the most conservative of the three parametric curves.

Table 4 Comparison of company log-logistic, log-normal and K-M plus exponential OS models with general UK population

	NIVO+IPI			Sunitinib		
	Log-logistic	Log-normal	K-M+ exponential	Log-logistic	Log-normal	K-M+ exponential
Time when mortality rates equal general mortality rate (cure point)	19 years	19 years	31 years	20 years	21 years	36 years

Source: Company model; ERG calculations

A final comment is that the ERG noted in its critique of the company response to the ACD that patients treated with sunitinib in the Checkmate 214 trial were allowed to crossover onto the NIVO+IPI arm following a protocol amendment in November 2017. It was not clear in the company in response to the ACD how the crossover issue had been addressed and this issue remains in the CDF proposal. The ERG considers that it would have been beneficial for this CDF proposal to include an analysis plan that examines the effect of crossover on OS.