NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for previously treated advanced renal cell carcinoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using nivolumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 26 July 2016

Second appraisal committee meeting: 4 August 2016

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Nivolumab is not recommended within its marketing authorisation for previously treated advanced renal cell carcinoma in adults.

1.2 This guidance is not intended to affect the position of patients whose treatment with nivolumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Nivolumab (Opdivo, Bristol–Myers Squibb) is a human monoclonal antibody that blocks an immune checkpoint protein receptor called programmed cell death protein 1 (PD-1) to promote an anti-tumour response.
Marketing authorisation	Nivolumab 'as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults'. Before the marketing authorisation was granted (May 2016), nivolumab was available in the NHS through the early access to medicines scheme.
Adverse reactions	The most common adverse reactions with nivolumab in clinical trials were tiredness, rash, pruritus, diarrhoea, nausea and decreased appetite (occurring in more than 10% of people). For full details of adverse reactions and contraindications, see the summary of product

	characteristics.
Recommended dose and schedule	3 mg/kg given intravenously every 2 weeks.
Price	The list price is £439 per 40-mg vial or £1,097 per 100-mg vial. Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Bristol–Myers Squibb and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of nivolumab, having considered evidence on the nature of renal cell carcinoma (RCC) and the value placed on the benefits of nivolumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee considered the experience of people with advanced RCC. It heard from the clinical and patient experts that nivolumab could possibly extend life and improve its quality. It heard that nivolumab was generally well tolerated, and usually caused fewer side effects than other treatments such as axitinib and everolimus. The committee noted that 1 of the patient experts was having nivolumab and was able to continue working. The committee heard that people prefer oral treatments that they can have at

home, but are willing to travel to have intravenous infusions to get effective therapy.

Treatment pathway

4.2 The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced RCC would be offered one of two tyrosine kinase inhibitors (TKIs); either pazopanib or sunitinib, as recommended in NICE's technology appraisals. If the disease progresses and they are fit enough to have further treatment, most people are then offered a different TKI, axitinib, as recommended in NICE's technology appraisal guidance. The committee understood that everolimus (a mammalian target of rapamycin [mTOR] inhibitor) is currently available through the Cancer Drugs Fund for people who have had treatment with only 1 TKI and for whom axitinib is contraindicated or not tolerated. It heard from the clinical experts that, if given a choice of axitinib or everolimus for previously treated RCC, they would prefer axitinib because they expect a better response to a second TKI than an mTOR inhibitor. The committee heard that, in current practice, everolimus is offered to people who have previously had TKI-related adverse events such as hypertension, or who cannot tolerate axitinib, or for whom axitinib is contraindicated. The committee heard that after 2 treatments, no further treatments are available in the NHS and people are offered best supportive care.

Comparators

4.3 The committee heard from the clinical experts that they would like to use nivolumab for people who have had 1 or 2 previous treatments. The experts also advised that a small number of people cannot tolerate axitinib or everolimus, but may be able to have nivolumab because of its favourable toxicity profile. For people who have had 1 previous treatment, the committee agreed that the relevant comparator for nivolumab is:

- axitinib, for most people

- everolimus, for people who cannot have axitinib
- best supportive care, for people who cannot have axitinib or everolimus.

The committee further concluded that, for people who have had 2 previous treatments, best supportive care is the appropriate comparator for nivolumab.

Clinical effectiveness

Survival benefit of nivolumab compared with everolimus

4.4 The committee noted that the evidence for nivolumab mostly came from CheckMate 025, a well-conducted open-label randomised controlled trial with 821 patients that compared nivolumab with everolimus. Overall survival was the primary outcome. The committee noted that, in CheckMate 025, patients randomised to nivolumab lived longer (median 25.0 months) than patients randomised to everolimus (median 19.6 months; 95% confidence interval [CI] 17.6 to 23.1), resulting in a hazard ratio of 0.73 (98.5% CI 0.57 to 0.93; p=0.002). The committee recognised that the hazard ratio was calculated assuming proportional hazards. It agreed that a proportional hazard was not supported by the Kaplan–Meier plot for overall survival or the statistical test done by the evidence review group (ERG). The committee therefore agreed that the hazard ratio may not be robust. The committee noted that the CheckMate 025 trial showed no difference in progression-free survival between nivolumab and everolimus. The committee concluded that, compared with everolimus, nivolumab extended overall survival but not progression-free survival.

4.5 The committee considered the extent to which nivolumab extends survival when compared with everolimus, noting:

- The CheckMate 025 trial stopped early after an interim analysis showed a survival benefit; the committee was aware that trials which

stop early because they show a benefit tend to overestimate the size of the treatment effect. It considered the survival data from CheckMate 025 to be immature because, at the time of the interim analysis that led to the study stopping (July 2015), 398 out of 821 (48%) patients had died and median follow-up was only about 18 months.

- The company's submission stated that, when nivolumab is used to treat melanoma, survival curves show 'long tails' for overall survival meaning that most patients die early but some patients survive for a long time. The clinical experts advised that it was plausible that an overall-survival curve with a 'long tail' would also be shown for RCC treated with nivolumab.
- In the clinical experts' opinion, the follow-up data from CheckMate 003 and CheckMate 010 (phase I and II trials of nivolumab in RCC) supported this hypothesis. The committee noted that CheckMate 003 (n=34) showed that 34% of patients having nivolumab were alive after 5 years, while CheckMate 010 (n=168) showed that 44% were alive after 3 years, but observed that the trial populations were small and it was not clear whether the patients in these trials were like those in the NHS. The committee noted that the company chose not to use these data to inform its economic model (instead using CheckMate 025).
- CheckMate 025 data showed that only about 15% of patients were still having nivolumab after 2 years. The committee considered that when median survival with nivolumab was just over 2 years (25 months; see section 4.5), it was implausible to assume that more than a few people would live to 5 years.

The committee concluded that the most robust results came from the large CheckMate 025 trial, which showed that nivolumab extended life by a median of 5.4 months compared with everolimus, but that there was substantial uncertainty about the extent of the survival benefit when measured over the long term.

Generalisability of the CheckMate 025 population

4.6 The committee heard from the clinical experts that the characteristics of the patients in CheckMate 025 were similar to those of the people in their NHS clinics. The committee concluded the trial results were generalisable to the NHS but it was uncertain whether nivolumab was equally effective in all subgroups of patients.

Subgroups with 1 or 2 previous treatments

4.7 The committee recognised that the trial included a mix of people who had had 1 previous treatment (72% of patients) and people who had had 2 previous treatments (28%). During the committee meeting, the company stated that a subgroup analysis showed that the treatment effect of nivolumab compared with everolimus was clinically and statistically significant both for patients who had 1 previous treatment (HR 0.79) and 2 previous treatments (HR 0.65), and that there was no interaction. After the committee meeting, the committee chair noted that the hazard ratios in a published paper (Motzer et al. 2015) were different and showed no statistically significant benefit for patients who had already had 2 previous treatments. Also, the test for an interaction between subgroup and treatment effect was not specified in the published statistical plan. The committee concluded that it was uncertain whether the survival benefit seen in the overall trial population would apply equally to all NHS patients, regardless of the number of previous treatments. It invited the company to clarify this in its response to the appraisal consultation document.

Subsequent treatments in CheckMate 025

4.8 The committee was aware that people generally have nivolumab until disease progression, or some time beyond it, after which some people try other therapies. The committee heard from the company that patients could not switch treatments during the trial (that is, patients randomised to everolimus could not have nivolumab after progression), yet patients in both the nivolumab and everolimus groups had subsequent treatments

including everolimus and TKIs. The committee heard from the clinical experts that these subsequent treatments extend survival, but that they are not given in NHS practice after people have had 2 treatments. The committee recognised the use of these treatments may not have been equal between both groups in CheckMate 025, which may confound the results, although the direction of the bias was not clear. The committee concluded that this should be taken into account in any analyses and so ideally the economic model for nivolumab should exclude both the costs and benefits of subsequent treatments.

Duration of nivolumab treatment

4.9 The committee noted that the summary of product characteristics and the trial allowed nivolumab treatment to continue after disease progression. It heard from the clinical experts that about 10% of people have treatment for a short time after disease progression. The committee concluded that treatment after disease progression was likely to happen in NHS practice and had been appropriately included in the economic model.

Network meta-analysis

4.10 The committee understood that, because there were no head-to-head trials comparing nivolumab with axitinib or best supportive care, the company had done a network meta-analysis to compare the treatments indirectly. To compare nivolumab with best supportive care, the network linked CheckMate 025 (nivolumab compared with everolimus) with the RECORD-1 trial (everolimus compared with best supportive care) using everolimus as a common comparator. To compare nivolumab with axitinib, the network joined these 2 trials to 2 other trials (TARGET, best supportive care compared with sorafinib; AXIS, sorafenib compared with axitinib). It noted advice from the evidence review group (ERG) that the results were likely to be biased because of differences between trials:

- **Number of previous treatments**: CheckMate 025 recruited patients who had had 1 or 2 previous treatments, while the other trials recruited patients who had only had 1 previous treatment.
- **Choice of previous treatments**: The committee heard from the clinical experts that previous therapy affects the condition's response to subsequent treatments. The committee acknowledged that the company had partly addressed this by only using data from the subgroup of patients in the AXIS trial who previously had sunitinib. But the trials still differed in the choice of previous treatments.
- **Prognosis of patients at baseline**: The committee noted that patients in AXIS had a poorer prognosis than those in CheckMate 025, measured using the Memorial Sloan Kettering Cancer Center (MSKCC) tool for predicting renal cancer prognosis. The committee heard from the company that both trials used the MSKCC tool, but that 1 component (performance status) was measured using different tools in each trial. The company stated that this explained the difference in prognosis and that the trial populations were, in fact, similar. The committee concluded that there was no way to assess whether the prognosis of the trial patients was similar. The committee also heard during the meeting that the company had adjusted its network meta-analysis to account for differences in baseline risk between trial populations, but the company did not give details and had not included this information in its submission.
- **The methods used to adjust for treatment crossover**: The committee was aware that the company preferred to use 'crossover-adjusted' hazard ratios to inform the network meta-analysis, but that the method of adjustment differed between the TARGET trial and the RECORD-1 trial. While the committee acknowledged that the analysis of each individual trial was outside the control of the company, it remained concerned that the network meta-analysis used intention-to-treat results from both AXIS and Checkmate 025 with no adjustment for

the subsequent treatments which patients had in those trials, but used adjusted results from TARGET and RECORD-1.

4.11 The committee assessed the effect of the limitations in the network meta-analysis. It heard from the ERG that the poorer prognosis of patients in AXIS, and not adjusting for subsequent treatments in that trial, meant that the results were likely to underestimate the effectiveness of axitinib, and so overestimate the effectiveness of nivolumab. The committee concluded that the company's network meta-analysis was likely to be biased in favour of nivolumab.

Effectiveness of axitinib compared with everolimus (and, by extension, nivolumab)

4.12 The committee was aware that to estimate the relative effectiveness of nivolumab and axitinib, the economic model used the results of Checkmate 025 (nivolumab compared with everolimus) but adjusted the everolimus arm, using the network meta-analysis, such that it represented the effectiveness of axitinib. Two key inputs to the economic model were therefore the hazard ratios for progression-free survival and overall survival comparing axitinib with everolimus. The committee noted that the company's network meta-analysis showed axitinib was less effective than everolimus (the results are academic-in-confidence and cannot be reported here). The committee questioned the face-validity of this result.

- It heard from clinical experts that in their experience, axitinib and everolimus have similar treatment effects.
- The committee also heard that clinicians would usually choose axitinib over everolimus (unless a person could not tolerate TKIs) because they expected a better response with a second TKI than with an mTOR inhibitor.
- The committee noted that a published indirect treatment comparison of axitinib and everolimus showed no difference in progression-free survival (Sherman et al. 2015).

The committee acknowledged the limited evidence, but concluded that axitinib and everolimus were likely to have similar effectiveness and that it was appropriate to use a hazard ratio of 1 for overall survival and progression-free survival in the model. The committee agreed that nivolumab was likely to extend survival compared with axitinib, but noted that because the company's economic model assumed that patients on everolimus lived longer than patients on axitinib, the model probably overestimated the effectiveness of nivolumab compared with axitinib.

Cost effectiveness

4.13 The committee agreed that the structure of the 6-stage, partitioned-survival economic model was appropriate. It noted that the model represented patients who had had either 1 or 2 previous treatments and the company did not present separate analyses for patients who had 1 previous treatment and patients who had 2 or more therapies. The committee preferred to consider these subgroups separately because the comparators that reflect NHS practice differ for each group (see section 4.3) and the patients in the groups likely differ in ways that might affect treatment effectiveness.

Modelling overall survival

4.14 The committee was concerned that, because the trial data were immature (see section 4.5), a large proportion of the overall-survival benefit was based on extrapolation rather than on trial data. The committee was aware that, for predicting overall survival with nivolumab and everolimus, the company fitted a generalised gamma model to extrapolate the data from CheckMate 025. The committee noted that this model relies on the 'accelerated failure-time' assumption, but this assumption had not been formally tested by the company. In the committee's opinion, the survival curves converged suggesting that the assumption was not met. The committee noted that an alternative approach is to fit independent models to each treatment group (that is, separate models for nivolumab and

everolimus), but the company had chosen not to do this. Because the company had not presented any alternative approaches, the committee used the generalised gamma model for decision-making. However, the committee remained concerned that the assumptions underpinning the model were not met and it could not assess the impact on the results of using independent models.

4.15 The committee discussed the company's scenario analysis that assumed a longer-term survival benefit for nivolumab (see section 4.5). Instead of using trial data, this analysis assumed that patients having nivolumab, who survived for 5 years, would have the same risk of death after 5 years as the age matched general population. This analysis reduced the company's base case ICER for nivolumab compared with axitinib from £42,417 to £22,923 per QALY gained (note that this analysis uses the list price of axitinib and contains minor modelling errors). The committee noted that it had not seen any evidence to support the assumption in the company's scenario analysis, and it was not clear how this scenario compared with the long term data from CheckMate 003 and CheckMate 010. The committee concluded that the company's scenario assuming better long-term survival with nivolumab was not based on evidence, so it preferred to use trial data to estimate survival as had been done in the company's base case and the ERG's base case.

Modelling time-to-stopping treatment

4.16 The committee noted that the company fitted a complex spline model to predict time-to-stopping treatment with nivolumab and everolimus. The committee agreed with the ERG that the company had not justified its choice of a complex model, and a simpler approach may be more appropriate because additional complexity increases uncertainty. The committee noted that the ERG's analyses used a log-normal distribution and this slightly decreased the company's base-case incremental cost-effectiveness ratio (ICER) for nivolumab compared with axitinib from £43,109 to £42,599 per quality-adjusted life year (QALY) gained, using

the list price of axitinib rather than its confidential discounted price. The committee noted the ERG's advice that a generalised gamma distribution also fitted the data well, and increased the ERG's ICER. The committee considered that the simpler models used by the ERG appeared to fit the data better at the beginning of the trial, but less so at the end. Overall the committee preferred to use either a log-normal or a generalised gamma distribution to predict time-to-stopping treatment, but was not confident that any of the curves presented by the company or the ERG provided a good fit to the entire Kaplan-Meier curve.

Cost of nivolumab

4.17 The committee noted that the costs of delayed doses had been excluded from the company's model. The committee heard that, in CheckMate 025, about 5% of doses were delayed and the average delay was 2 weeks. The committee was aware that nivolumab is given every 2 weeks and so, in the company's opinion, the NHS would not incur any costs from 'delayed' doses because these were, in effect, missed doses. The committee remained concerned that, if a planned dose was delayed for a short time, the dose would still be given and this would incur a cost for the NHS. The committee was aware that the ERG's analysis, which included the costs of missed and delayed doses, increased the company's base-case ICER for nivolumab compared with axitinib from £43,109 to £48,375 per QALY gained, using the list price of axitinib. The committee concluded that the true cost to the NHS of providing nivolumab probably lay between the assumptions used by the company (excluding missed and delayed doses) and the ERG (including missed and delayed doses).

Cost of subsequent treatments

4.18 The committee noted that the company's model included the costs of subsequent treatments, based on the treatments used in CheckMate 025. It recalled that these treatments are believed to have a survival benefit (see section 4.8) but are not used in the NHS. The committee would have

preferred to see an analysis that excluded both the costs and the clinical benefits of subsequent treatments, but the company had not presented this analysis. The ERG presented an analysis that removed the costs of subsequent treatments, but the committee agreed that this was not appropriate because the clinical benefits were still included in the model. The committee concluded that, because all the analyses included the clinical benefits of subsequent treatments, it preferred to also include the costs of those treatments.

Utility values

4.19 The committee was aware that CheckMate 025 collected health-related quality-of-life data using EQ-5D. The company took utility values for its model from CheckMate 025 for nivolumab and everolimus, and from AXIS for axitinib; the AXIS utilities were lower. It considered that the benefits reported by patients, such as fewer side effects with nivolumab, were captured in the utility values taken from the CheckMate 025 trial. But, the committee recognised that the trial was open-label, which may mean that patients overestimate the utility benefit of novel treatments such as nivolumab. The committee did not find the company's utility values plausible because:

- The post-progression utility values for patients who had nivolumab and everolimus were higher than the pre-progression utility values for patients having axitinib or best supportive care.
- The model assumed that, even after disease progression and stopping treatment, there was a constant benefit of having been treated with nivolumab rather than axitinib or everolimus. The committee heard from the clinical experts that a post-progression treatment benefit may exist, because the adverse effects experienced with axitinib or everolimus take some time to resolve, but that these differences would only be seen for a short time.

- The utility values were lower for axitinib than for everolimus, but the committee heard from the clinical experts that in their experience, health-related quality of life was similar for people whose condition was being treated with these drugs.

The committee concluded that the company's utility values were not appropriate. It noted that some of the ERG's analyses used the same utility values for axitinib, everolimus and best supportive care; the committee agreed that this was more appropriate than applying different utility values for axitinib and everolimus. The committee was still concerned that the model assumed an extended post-treatment benefit of nivolumab and it had not been presented with analyses that excluded this benefit.

4.20 The committee had agreed that the model should use the same utility values for axitinib and everolimus (see section 4.19), and it noted that the ERG had presented 2 analyses that did this. The first analysis took utility values for axitinib and best supportive care from the everolimus group in CheckMate 025; this increased the company's base-case ICER for nivolumab compared with axitinib from £43,109 to £50,946 per QALY gained, using the list price of axitinib. The second analysis took utility values for all treatments from the axitinib group in AXIS; the gain in utility for nivolumab compared with everolimus was taken from CheckMate 025. This increased the company's base-case ICER for nivolumab compared with axitinib to £56,315 per QALY gained. The committee concluded that either of these approaches was preferable to the company's base case.

Results of cost-effectiveness analyses

4.21 The ERG corrected minor errors in the company's model; this document presents the corrected results. The company presented pairwise comparisons. In the company's base case the deterministic ICER was £43,109, £86,136 and £57,096 per QALY gained for nivolumab compared with axitinib (at list price), everolimus and best supportive care

respectively (table 1). The company's base case ICER for nivolumab compared with axitinib increased to more than £50,000 per QALY gained when the confidential discount for axitinib was included (these results are confidential and cannot be presented here). The committee noted that the company's base case did not include many of its preferred assumptions. The committee's preferred analysis:

- assumed axitinib was as effective as everolimus for progression-free survival and overall survival (ERG's preferred base case; see section 4.12)
- used a log-normal distribution to model time-to-stopping treatment (ERG's preferred base case; see section 4.16)
- assumed utility values for axitinib and everolimus were equal (ERG's preferred base case; see sections 4.19 and 4.20)
- included the costs of subsequent therapy (company's base case; see section 4.18).

The committee agreed that it would be more appropriate to consider separate analyses for the subgroups of patients who had had either 1 or 2 previous treatments, but the company had not presented these analyses.

4.22 The committee noted that, in the ERG's preferred base case, the ICER increased to more than £60,000 per QALY gained for nivolumab compared with each comparator (table 1). The ERG's preferred base-case ICER for nivolumab compared with axitinib was £74,132 per QALY gained, and this increased even more when the confidential discount for axitinib was included. The committee acknowledged that the ERG's preferred base case overestimated the ICERs because it excluded subsequent therapy costs and included the costs of all missed and delayed doses, so the most plausible ICER lay between the company and ERG estimates. Nonetheless, all of the ICERs presented by the company and the ERG exceeded £50,000 per QALY gained when the axitinib discount was included. The committee concluded that, compared with any

comparator, the ICER for nivolumab was substantially above the range that could be considered a cost-effective use of NHS resources.

Table 1 Pairwise analysis of the company's base case and ERG's preferred base case

Treatment	Total values		Increments		Company's base-case ICERs	ERG's preferred base case ICER
	Costs (list price)	QALYs	Costs	QALYs		
Nivolumab	£91,326	2.30	–	–	–	–
Axitinib	£46,113	1.25	£45,213	1.05	**£43,109**	**£74,132**
Everolimus	£38,933	1.69	£52,393	0.61	**£86,136**	**£91,989**
Best supportive care	£10,525	0.88	£80,801	1.42	**£57,096**	**£61,317**
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.						

Innovation

4.23 The committee considered whether nivolumab was an innovative treatment. It heard from patient experts that nivolumab represented a step change in terms of extension to life and the quality of life while on treatment. The committee agreed that nivolumab was an innovative treatment in RCC, but noted that it was not the first checkpoint inhibitor to gain a marketing authorisation for treating cancer. It also noted that before the marketing authorisation was granted, nivolumab was available for people in the NHS through the early access to medicines scheme, which aims to give patients access to promising innovative medicines and is granted by the UK Medicines and Healthcare products Regulatory Agency (MHRA). The committee concluded that it had not been presented with any evidence of additional benefits of nivolumab that were not captured in the QALY measure.

End-of-life considerations

4.24 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods.

4.25 The committee discussed whether nivolumab met the end-of-life criteria. It first discussed the life expectancy of people with previously treated advanced RCC having all 3 comparator treatments:

- Patients having axitinib lived for about 20 months (population studies, trial data).
- Patients having everolimus lived for about 19.6 months (CheckMate 025).
- Patients having best supportive care lived for less than 12 months (population studies, trial data).

Although data on mean life expectancy were not available, on the balance of the evidence the committee concluded that average life expectancy was less than 24 months for people with advanced RCC and that the life-expectancy criterion was met.

4.26 The committee discussed whether nivolumab extended life by at least 3 months, noting that the relevant comparators depended on treatment history (see section 4.3). For people who had 1 previous treatment the committee compared nivolumab with axitinib, everolimus and best supportive care. For people who had had 2 previous treatments it compared nivolumab with best supportive care. The committee recognised that the estimates of extensions to life were based on the overall trial population in CheckMate 025, which included a mixture of patients who had had 1 previous treatment and those who had had 2 previous treatments. The committee observed that CheckMate 025 had shown a median increase in survival of 5.4 months compared with everolimus. The committee had assumed axitinib was similarly effective to

everolimus and so accepted that the extension to life for people having axitinib would also be greater than 3 months. The committee assumed that any extension to life would be even longer for nivolumab compared with best supportive care for people who had had 1 and 2 previous treatments. The committee therefore agreed that nivolumab met the end-of-life criteria.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.27 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Conclusion

4.28 The committee noted that the company's base case ICER for nivolumab was more than £50,000 per QALY gained compared with any comparator. The ERG's ICERs were over £60,000 per QALY gained (see section 4.22). The committee concluded that, even when applying the maximum weighting to the QALY that is possible under the end-of-life criteria, the ICER for nivolumab did not fall within the range of a cost-effective treatment. Therefore, the committee could not recommend nivolumab as a cost-effective use of NHS resources.

Cancer Drugs Fund

4.29 Having concluded that nivolumab could not be recommended for routine use, the committee then considered if nivolumab could be recommended

for treating RCC within the Cancer Drugs Fund. The committee considered whether nivolumab had the plausible potential to be cost effective at its list price in any clinical scenarios that were more optimistic than the company's base case. The clinical experts advised that a 'long survival tail' had been seen with nivolumab in melanoma and the committee accepted the theoretical possibility that this could also occur in RCC (see section 4.5). The committee noted that the company's scenario analysis assuming an extended survival benefit in some patients dramatically reduced the company's ICER for nivolumab compared with axitinib (see section 4.15). However, the committee was not presented with an analysis that combined a 'long survival tail' with its preferred assumptions.

4.30 The committee recognised that additional data on the survival benefit of nivolumab in the long term would reduce clinical uncertainty and could improve cost effectiveness. It acknowledged that data collected from patients within the Cancer Drugs Fund was unlikely to have a long enough follow-up period. The committee heard during the meeting that the company was continuing to collect survival data from CheckMate 025, and it agreed that this study presents the best opportunity for measuring long-term survival with nivolumab. However, the company did not explain how many patients were still being followed up or the timing of the planned analyses. Thus, the committee was uncertain if the analyses would be conducted within the limited timeframe of the Cancer Drugs Fund (usually 24 months). The committee concluded that it would be willing to consider a proposal for nivolumab to be funded through the Cancer Drugs Fund, but only if:

- the company was able to show plausible potential for cost-effectiveness using the committee's preferred assumptions in the economic model, and

- the company provided detailed evidence of how CheckMate 025 will address the uncertainty around long-term survival within a limited time period.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Nivolumab for treating advanced renal cell carcinoma after prior therapy in adults**	**Section**
Key conclusion		
Nivolumab is not recommended within its marketing authorisation for previously treated advanced renal cell carcinoma in adults. Nivolumab extended overall survival compared with everolimus, but there was substantial uncertainty about the extent of the survival benefit when measured over the long term. The evidence review group's (ERG's) incremental cost-effectiveness ratio (ICER) for nivolumab compared with any comparator was more than £60,000 per quality-adjusted life year (QALY) gained. The committee concluded that, even when applying the maximum weighting to the QALY that is possible under the end-of-life criteria, the ICER for nivolumab did not fall within the range of a cost-effective treatment.		1.1 4.4, 4.5 4.22, table 1
Current practice		

Clinical need of patients, including the availability of alternative treatments	People with newly diagnosed advanced renal cell carcinoma are usually offered one of two tyrosine kinase inhibitors (TKIs); either pazopanib or sunitinib. If the disease progresses and they are fit enough to have further treatment, most people are then offered a different TKI; axitinib. Everolimus is currently available through the Cancer Drugs Fund for people who have had treatment with only 1 TKI and for whom axitinib is contraindicated or not tolerated. The committee heard that after 2 treatments, no further treatments are available in the NHS and people are offered best supportive care.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Nivolumab extends life compared with everolimus. Patient experts advised that nivolumab usually causes fewer side effects than other treatments such as axitinib and everolimus. Before the marketing authorisation was granted, nivolumab was available through the early access to medicines scheme. The committee agreed that nivolumab was an innovative treatment in renal cell carcinoma, although it was not the first checkpoint inhibitor to gain a marketing authorisation for treating cancer.	4.4 4.1 4.23

What is the position of the treatment in the pathway of care for the condition?	For people who have had 1 previous treatment, nivolumab is a potential alternative to: • axitinib (which is offered to most people) • everolimus (which is offered to people who cannot have axitinib) • best supportive care (which is offered to people who cannot have axitinib or everolimus). For people who have had 2 previous treatments, nivolumab is a potential alternative to best supportive care.	4.3
Adverse reactions	The most common adverse reactions with nivolumab are tiredness, rash, pruritus, diarrhoea, nausea and decreased appetite.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The evidence mostly came from CheckMate 025, an open-label randomised trial with 821 patients that compared nivolumab with everolimus. The company provided unpublished data from a phase I and a phase II trial (CheckMate 003 and CheckMate 010 respectively); these trials included longer-term follow-up data on mortality.	4.4, 4.5

Relevance to general clinical practice in the NHS	The committee concluded that the overall trial population was similar to NHS patients and so the results were generalisable to the NHS.	4.6
Uncertainties generated by the evidence	The CheckMate 025 data were immature. The clinical experts advised that it was plausible that in the future an overall-survival curve with a 'long tail' (that is, an extended survival benefit) would be shown for renal cell carcinoma treated with nivolumab, based on the results of nivolumab for melanoma. Having considered the evidence presented, the committee agreed it was implausible to assume that more than a few people would live to 5 years. The committee concluded that the most robust results came from CheckMate 025, which showed that nivolumab extended life by a median of 5.4 months compared with everolimus, but that there was substantial uncertainty about the extent of the survival benefit when measured over the long term.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	CheckMate 025 included a mix of people who had had 1 previous treatment and people who had had 2 previous treatments. During the committee meeting, the company stated that the treatment effect of nivolumab was clinically and statistically significant for both subgroups. After the meeting, the committee chair noted that the hazard ratios in a published paper (Motzer et al. 2015) were	4.7

	different and showed no statistically significant benefit for patients who had had 2 previous treatments. The committee concluded that it was uncertain whether the survival benefit seen in the overall trial population would apply equally to all people, regardless of the number of previous treatments. It invited the company to clarify this.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	CheckMate 025 showed that nivolumab extended life by a median of 5.4 months compared with everolimus, but there was substantial uncertainty about the extent of the survival benefit when measured over the long term.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The company presented a 6-stage, partitioned-survival economic model comparing nivolumab with axitinib, everolimus and best supportive care.	4.13

Uncertainties around and plausibility of assumptions and inputs in the economic model	The estimates of overall survival for nivolumab were uncertain because the CheckMate 025 trial data were immature. The company presented a scenario assuming that patients who survived for 5 years, would have the same risk of death after 5 years as the age-matched general population; this reduced the ICER for nivolumab compared with axitinib from £42,417 to £22,923 per QALY gained. However, the committee had not seen evidence to support this assumption. Based on a network meta-analysis, the company's model assumed that axitinib was less effective than everolimus. The network meta-analysis was highly uncertain. So, in line with clinical opinion, the committee preferred to assume that axitinib and everolimus had the same effectiveness (as the ERG had done). It was uncertain whether the NHS would incur the costs of delayed doses of nivolumab.	4.5, 4.15 4.12 4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-	The committee did not find the company's utility values plausible and it preferred the ERG's alternative assumptions around utility. The committee was not presented with any evidence of additional benefits of nivolumab that were not captured in the QALY measure.	4.19, 4.20 4.23

related benefits been identified that were not included in the economic model, and how have they been considered?		
Are there specific groups of people for whom the technology is particularly cost effective?	No subgroup analyses were presented.	
What are the key drivers of cost effectiveness?	• Overall survival with nivolumab • The effectiveness of axitinib compared with everolimus • The choice of distribution for modelling time-to-stopping treatment	4.14 4.12 4.16
Most likely cost-effectiveness estimate (given as an ICER)	When the confidential discount for axitinib was included, the ICER for nivolumab compared with any comparator was: • more than £50,000 using the company's base case • more than £60,000 using the ERG's base case. The most plausible ICER lay between the company and ERG estimates.	Table 1, 4.22
Additional factors taken into account		

Patient access schemes (PPRS)	There is no patient access scheme for nivolumab. The ERG presented analyses that included the confidential discount for axitinib.	
End-of-life considerations	Nivolumab met the end-of-life criteria.	4.25, 4.26
Equalities considerations and social value judgements	No equality issues were identified by consultees or the committee.	

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee B
July 2016

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anna Brett
Technical Lead

Rosie Lovett
Technical Adviser

Jeremy Powell
Project Manager

ISBN: [to be added at publication]