NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Decision problem

- What are the relevant comparators for nivolumab when it is used:
  - second-line
  - second-line for people contraindicated to or intolerant of axitinib
  - third-line?

Clinical effectiveness

- The company's network meta-analysis included trial populations that differed in baseline risk and the number and type of previous treatments. Is this analysis adequate to inform decision-making?
- Is axitinib less effective than everolimus (as shown in the company's network meta-analysis) or more effective (as suggested by the ERG's clinical experts)?

- Patients in the AXIS trial of axitinib had a poorer prognosis than patients in the CheckMate 025 trial of nivolumab. Which trial population is more generalisable to NHS patients? (This relates to the choice of utility values for modelling.)
- The trial and the model permit treatment with nivolumab after disease progression. In practice, how would clinicians and patients decide when to stop taking nivolumab?

Cost effectiveness

- Does the company's model represent second- or third-line use of nivolumab, or both?
- The company's method for estimating relative treatment effects and utility values assumes that the patient populations were similar in AXIS and CheckMate 025. Is that assumption appropriate?
- Is it appropriate to take utility values directly from trials which may differ in their populations?
- For predicting time to stopping treatment, should the model use a spline-based curve (as in the company's base case) or log-normal or generalised gamma curves (as in the ERG's analyses)?
- Should the model take estimates of relative effectiveness from the network meta-analysis (as in the company's base case) or assume that axitinib is as effective as everolimus (as in the ERG's analyses)?
- Does the company's base case reflect the number of doses of nivolumab that would be received in practice?
- Should the model include the costs of subsequent treatments?

End of life

- What is the life expectancy of people with previously treated advanced or metastatic renal cell carcinoma?
- Does nivolumab extend life compared with current NHS treatments?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of nivolumab within its

marketing authorisation for previously treated advanced or metastatic renal cell carcinoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with previously treated advanced or metastatic renal cell carcinoma (RCC).	As in the scope.	None.	Population described in submission is the same as the scope. CheckMate025 population largely in line with scope.
Intervention	Nivolumab.	As in the scope.	None.	None.
Comparison	• Axitinib • Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) • Best supportive care.	As in the scope.	The company considers axitinib the most relevant comparator in English clinical practice and it is therefore presented as the key comparison. Comparisons with everolimus and best supportive care are also included.	The ERG noted that axitinib is the most relevant comparator but that at the time the CheckMate 025 trial started everolimus was the only active treatment with a marketing authorisation for previously treated advanced RCC.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	As in the scope.	None.	None.

2 The technology and the treatment pathway

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) is a human monoclonal antibody that targets and blocks a receptor known as PD-1 (programmed cell death protein 1). Nivolumab has been available in the UK since February 2016, through the Early Access to Medicines Scheme, for patients with advanced renal cell carcinoma that has previously been treated. It received a marketing authorisation in May 2016[1] for treating advanced renal cell carcinoma after prior therapy in adults.

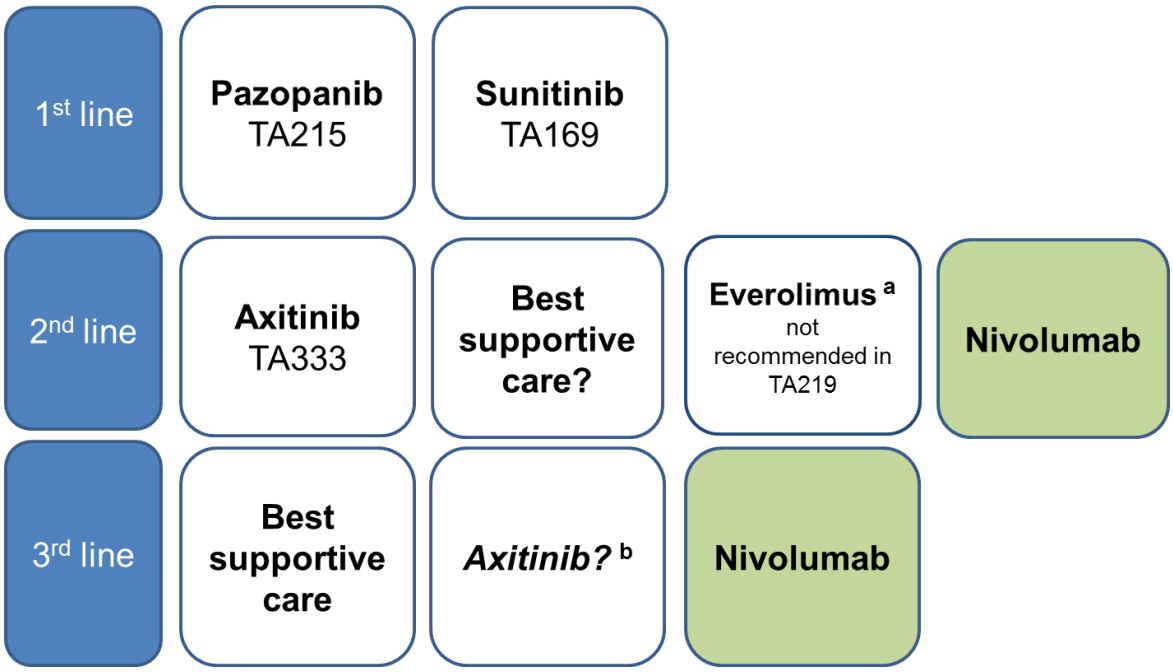
2.2 RCC is the most common type of kidney cancer and about 30% of people have advanced disease at the time of diagnosis. Current treatment options for advanced disease include:

- **Initial treatment:** NICE technology appraisal (TA) guidance recommends the tyrosine kinase inhibitors (TKI) pazopanib (TA215) or sunitinib (TA169).
- **Second treatment:**
  - NICE recommends axitinib (TA333). Although the marketing authorisation for axitinib specifies prior treatment with *sunitinib* or a cytokine, the committee for TA333 agreed that axitinib would be used for patients previously treated with either sunitinib or pazopanib (see TA333 sections 1 and 4.3).
  - Everolimus is not recommended by NICE (TA219), but it is available through the Cancer Drugs Fund for people who have had prior treatment with only 1 TKI, only if axitinib is contraindicated or not tolerated.

No third-line treatments are recommended by NICE. The company's treatment pathway suggests that nivolumab could be used as a second- or third-line treatment (figure 2).

[1] This was identified as an error after the committee meeting; marketing authorisation was received in April 2016.

Figure 1 Treatment pathway including nivolumab (adapted from figure 5, section 3.2 of company's submission)



Notes: a, everolimus is funded via the Cancer Drugs Fund for patients who had prior treatment with only 1 TKI, only if axitinib is contraindicated or not tolerated; b, TA333 did not consider third-line use of axitinib.

Table 2 Technology

	Nivolumab	Axitinib	Everolimus
Marketing authorisation	Nivolumab as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults	Axitinib is indicated for the treatment of adult patients with advanced renal-cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.	Everolimus is indicated for the treatment of patients with advanced renal-cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.
Administration method	3 mg/kg every 2 weeks administered by intravenous infusion.	5 mg oral tablet twice daily.	10 mg oral tablet once daily.
Cost	List price £439 for 40 mg vial or £1,097 for 100 mg vial. Average cost of a course of treatment is £66,426	List price £703.40 for 56 x 1 mg tablets, £2,110.20 for 56 x 3 mg tablets or £3,517 for 56 x 5 mg tablets. Axitinib is available to the NHS at a discounted	List price £2,250 for 30 x 5 mg tablets or £2,673 for 30 x 10 mg tablets.

	(£71,260 including administration costs).	price via a patient access scheme (see the confidential appendix to this document).	
See summary of product characteristics for details on adverse reactions and contraindications. Nivolumab information taken from table 3, section 2.3 of the company's submission. Comparator information taken from the European Medicines Agency and British National Formulary.			

3 Comments from consultees

3.1 A joint submission from several professional organisations advised that people with previously treated metastatic renal cell carcinoma are treated with either axitinib or everolimus. It noted that most patients experience side effects with these treatments. The submission advised that the current standard of care with tyrosine kinase inhibitors (such as pazopanib, sunitinib and axitinib) and a mammalian target of rapamycin (mTOR) inhibitor (such as everolimus) has improved outcomes for patients, but that the benefit of second-line and subsequent treatments is usually modest. The professional organisations commented that the CheckMate 025 trial showed that quality of life was better with nivolumab than with everolimus.

3.2 A patient organisation advised that there a no biomarkers to predict which patients will respond to which renal cell carcinoma treatments, so it is important for patients to have access to a range of effective treatments. Several people advised that their quality of life improved whilst taking nivolumab.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified 1 phase III open-label randomised controlled trial, CheckMate 025, that compared nivolumab with everolimus in adults with advanced renal cell carcinoma (RCC). Patients were randomised 1:1 to

have 3 mg/kg of nivolumab (n=410) intravenously every 2 weeks or 10 mg everolimus (n=411) orally every day. Patients in both groups could continue treatment after disease progression if experiencing clinical benefit and tolerating the drug. The trial was conducted at 146 sites in 24 countries, including the UK.

4.2 CheckMate 025 included patients who had:

- histologically confirmed advanced or metastatic RCC with a clear-cell component (NB: about 75% of all cases of RCC are clear-cell)
- measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST) v1.1
- received 1 or 2 previous regimes of antiangiogenic therapy (such as sunitinib).
- received no more than 3 total previous regimens of systemic therapy
- disease progression during or after the last treatment regimen and within 6 months before study enrolment
- Karnofsky performance status of 70 and above (higher scores reflect better health).

4.3 The trial excluded patients who had:

- metastasis to the central nervous system
- received previous treatment with an mammalian target of rapamycin (mTOR) inhibitor (such as everolimus)
- current treatment with glucocorticoids (more than 10 mg prednisone daily).

4.4 The median age of all patients in CheckMate 025 was 62 years (range 18 to 88) and most patients were white (88%) and male (75%). Across treatment groups, 72% of patients had received 1 previous anti-angiogenic therapy and 28% had received 2.

4.5 Overall survival was the primary outcome in CheckMate 025. Secondary outcomes included:

- progression-free survival, defined as the time from randomisation to disease progression or death from any cause
- objective response rate, defined as a complete or partial response
- incidence of adverse events
- health-related quality of life, assessed using EQ-5D and the Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) questionnaire.

4.6 The final analysis of overall survival was planned for after 569 deaths but the trial terminated early (after 398 deaths) because the pre-specified statistical boundary for overall survival benefit had been crossed and there were no new safety signals. This occurred in July 2015. Patients had a minimum follow-up of 14 months (median follow-up ranged from 17.2 to 18.3 across treatment groups).

4.7 The efficacy analysis (for example, overall survival) used the intention-to-treat population (all randomised patients, n=821) and the safety analysis used the per protocol population (all patients who had at least 1 dose of either treatment, n=803).

Clinical trial results

Table 3 Results of CheckMate 025 (section 4.7 of company's submission)

Outcome	Nivolumab (n=410)	Everolimus (n=411)
Overall survival		
Number of deaths	183	215
Median overall survival (95% CI), months	25.0 (21.8 to not estimable)	19.6 (17.6 to 23.1)
Hazard ratio (95% CI)	0.73 (0.57 to 0.93) p=0.002	
Progression-free survival		
Number of patients with progression or death	318	322
Median (95% CI), months	4.6 (3.7 to 5.4)	4.4 (3.7 to 5.5)
Hazard ratio (95% CI)	0.88 (0.75 to 1.03) p=0.11	

Figure 2 Kaplan-Meier plot for overall survival (figure 8, section 4.7 of company's submission)

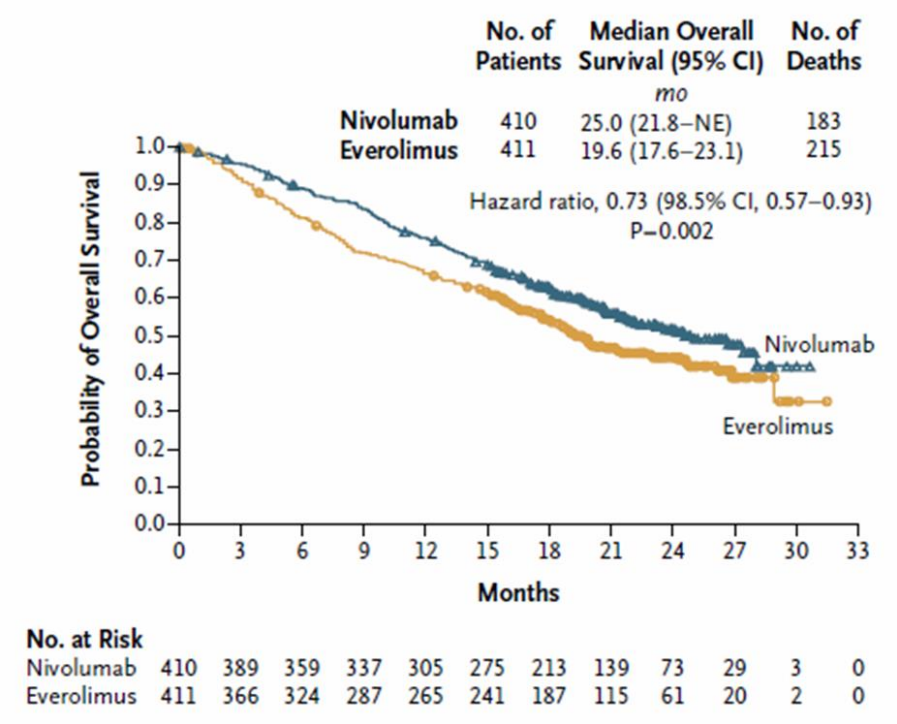
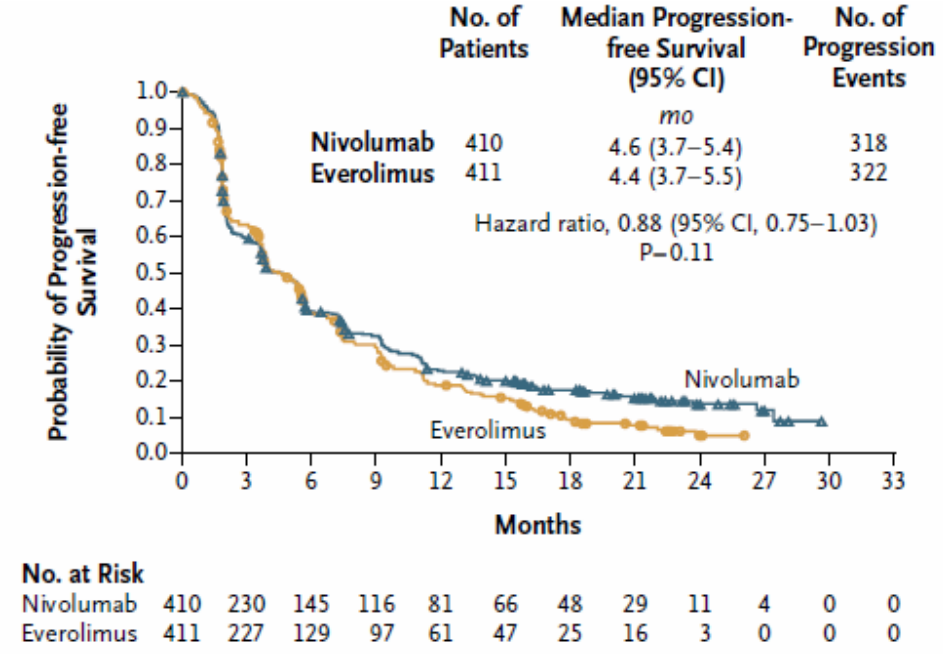


Figure 3 Kaplan-Meier plot for progression-free survival (figure 9, section 4.7 of company's submission)



4.8 The Kaplan–Meier curves showed that progression-free survival for both trial arms overlapped for 6 months before separating (see Figure 3). The

company advised that with immunotherapies like nivolumab, patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged initially (described as 'tumour flare'). In the company's opinion, using the RECIST criteria can underestimate the benefit of immunotherapy. The company also advised that, for melanoma, nivolumab shows a 'long tail' for overall survival, meaning that some patients survive for a long time after this immunotherapy. The company suggested that a long tail had not been observed for RCC because of insufficient follow-up and lack of statistical power.

Health-related quality of life

4.9 CheckMate 025 included EQ-5D as an 'exploratory endpoint'. The company advised that a between-group comparison of the median change from baseline in EQ-5D utility showed a statistically significant benefit of nivolumab compared with everolimus for weeks 8–12, weeks 24–44, weeks 52–68 and week 80. The NICE technical team noted that, for both treatment groups, the median change from baseline was smaller than 0.000 until week 96, and it was not clear whether the company's statistical analysis was adjusted for multiple comparisons (see appendix 6 of company submission).

4.10 The FKSI-DRS is a subscale of the 15-item FKSI; it contains 9 questions on lack of energy, pain, weight loss, bone pain, fatigue, dyspnoea, cough, fevers and haematuria. Scores range from 0 to 36, with 0 being the worst score. At baseline, the median FKSI-DRS score was 31.0 in both treatment groups. During the study 55% of patients in the nivolumab group experienced 'meaningful' FKSI-DRS improvement (defined as an increase of at least 2 points) compared with 37% of patients in the everolimus group ($p<0.001$).

ERG comments

4.11 The ERG noted that CheckMate 025 was an open-label trial and hence at risk of bias. Nonetheless, the ERG considered that CheckMate 025 was well designed and conducted. The ERG's clinical experts advised that

patients in CheckMate 025 had a better prognosis than patients with advanced RCC routinely seen in UK clinical practice. One of the ERG's clinical experts stated that patients in AXIS (a randomised open-label trial comparing axitinib with sorafenib) were more representative of the UK second-line patient population than those in CheckMate 025.

4.12 The ERG advised that it may be misleading to use a hazard ratio to summarise the treatment effect for overall survival and progression-free survival because the proportional hazards assumption was not met. That is, the ratio of the hazards in each treatment group was not constant over time. The ERG's clinical experts considered that the 'tumour flare' phenomenon described by the company was rarely seen in clinical practice.

Indirect treatment comparison

4.13 There were no head-to-head studies to compare nivolumab with either axitinib or best supportive care, so the company did a network meta-analysis. The company identified 18 trials from a systematic review and chose to include 9. There was no common comparator between the trials of nivolumab and axitinib, but these treatments were linked in the network by including trials of everolimus, placebo and sorafenib. This pre-meeting briefing, and the ERG's report, focuses on the 4 trials that informed the comparison of nivolumab with axitinib and best supportive care (CheckMate 025, RECORD-1, TARGET and AXIS; Figure 4. The company used placebo as a proxy for best supportive care. The company noted that the results of the network meta-analysis should be interpreted with caution because of differences in baseline risk and treatment history between the patients in each trial (see Table 4). For further information see table 16 in section 4.10.1 of the company's submission.

Figure 4 Company's network meta-analysis

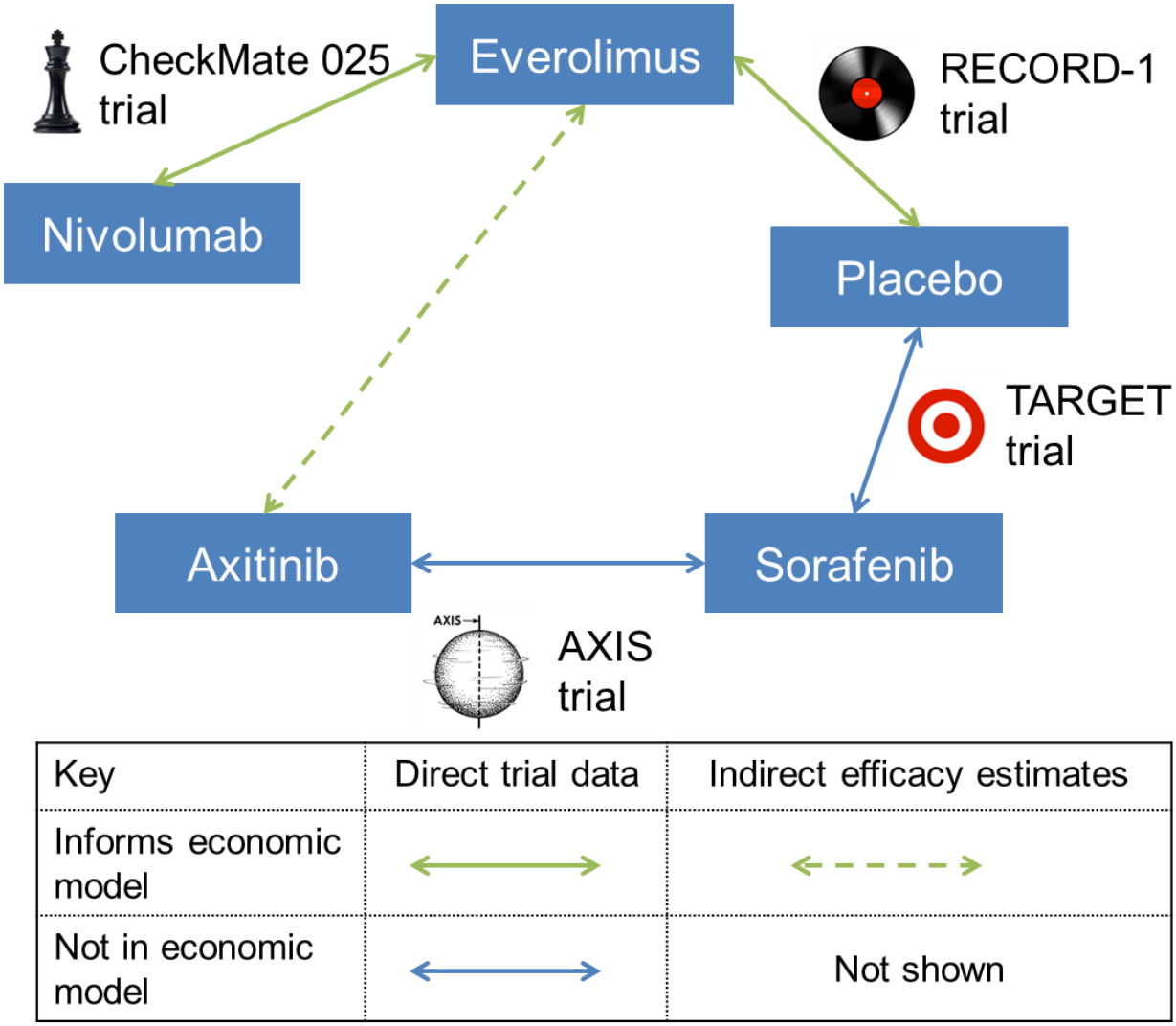


Table 4 Treatment history and baseline risk of patients in the trials (adapted from tables 19 and 20 in ERG's report and appendix 5 of company's submission)

Trial name	Permitted previous treatment	Line of treat-ment	MSKCC risk scores			
			Treatment group	Favourable	Intermediate	Poor
Check-Mate 025	Sunitinib Pazopanib Axitinib	2nd and post-2nd	Nivolumab	35%	49%	16%
			Everolimus	36%	49%	15%
AXIS	Sunitinib[a] Cytokines Bevacizumab Temsirolimus	2nd	Axitinib	28%	37%	33%
			Sorafenib	28%	36%	33%

RECORD -1	Sunitinib Sorafenib Cytokines (interferon, interleukin-2) Bevacizumab	2nd	Everolimus plus BSC	29%	56%	14%
			Placebo plus BSC	28%	57%	15%
TARGET	Cytokines (interferon, interleukin-2)	2nd	Sorafenib	NR	48%	52%
			Placebo	NR	49%	50%
Note: a, the company's network meta-analysis used the subgroup of patients in AXIS who had prior treatment with sunitinib. Abbreviations: BSC, best supportive care; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported						

4.14 The company presented 2 analyses for overall survival (see Table 5). The first used the intention-to-treat trial results. The 'crossover adjusted' analysis used:

- intention-to-treat results for CheckMate 025 and AXIS
- RECORD-1 results that were adjusted using the inverse probability of censoring weights method
- immature intention-to-treat results for TARGET, taken from an analysis before crossover was permitted.

The company used intention-to-treat trial results for progression-free survival.

Table 5 Results of the company's network meta-analysis

	Intention-to-treat HR (95% credible interval)	**Crossover-adjusted HR (95% credible interval)**
Overall survival		
Nivolumab vs axitinib	[redacted]	[redacted]
Nivolumab vs placebo	[redacted]	[redacted]
Progression-free survival		
Nivolumab vs axitinib	[redacted]	[redacted]
Nivolumab vs placebo	[redacted]	[redacted]
HR, hazard ratio; NA, not applicable		

ERG comments

4.15 The ERG considered the results of the network meta-analysis to be very uncertain because:

- The eligibility criteria of the trials differed in which prior treatments they permitted and the number of previous treatments (see Table 4).
- The participants in CheckMate 025 had a better prognosis than the participants in AXIS (see Table 4).
- The company took a crossover-adjusted hazard ratio from the published literature for RECORD-1, but did not assess whether appropriate methods were used to adjust for crossover.
- Most patients in AXIS had subsequent treatments after stopping the study drug, but the results were not adjusted to reflect the benefit of subsequent treatments.
- The company's 'cross-over adjusted' network meta-analysis used immature survival data from TARGET (which compared sorafenib with placebo).
- Only RECORD-1 assessed disease progression independently; in the remaining 3 trials the site investigators assessed progression.

4.16 The company's network meta-analysis showed everolimus is more effective than axitinib. The ERG's clinical experts thought this was implausible; indeed, they considered axitinib to be more effective. The ERG advised that the network meta-analysis may underestimate the effectiveness of axitinib because the company did not account for subsequent treatments in AXIS and used immature data for TARGET. A further estimate of the relative efficacy of everolimus and axitinib was provided by Sherman et al. (2015). This weight-adjusted indirect comparison compared the 2 treatments using data from RECORD-1 and AXIS, and found that median progression-free survival was similar (4.7 months with everolimus; 4.8 months with axitinib).

Adverse effects of treatment

4.17 The company analyses adverse events of any cause in CheckMate 025. More patients treated with nivolumab than with everolimus reported the grade 3-4 adverse events of hypercalcaemia (3% versus 0.5%), increased alanine aminotransferase (3% versus 0.3%) and malignant neoplasm progression (3% versus 1%). More patients treated with everolimus than with nivolumab reported anaemia (13% versus 6%), hyperglycaemia (6% versus 3%), hypertriglyceridemia (6% versus 0.7%), stomatitis (5% versus 0), and mucosal inflammation (4% versus 0). Treatment-related adverse events are shown in Table 6.

Table 6 Summary of treatment-related adverse events in CheckMate 025 (adapted from table 24, section 4.12 of company's submission)

	Nivolumab (n=406)		Everolimus (n=397)	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All TRAEs, n (%)	319 (78.6)	76 (18.7)	349 (87.9)	145 (36.5)
Fatigue	134 (33.0)	10 (2.5)	134 (33.8)	11 (2.8)
Stomatitis	8 (2.0)	0	117 (29.5)	17 (4.3)
Anaemia	32 (7.9)	7 (1.7)	94 (23.7)	31 (7.8)
Diarrhoea	50 (12.3)	5 (1.2)	84 (21.2)	5 (1.3)
Decreased appetite	48 (11.8)	2 (0.5)	82 (20.7)	4 (1.0)
Rash	41 (10.1)	2 (0.5)	79 (19.9)	3 (0.8)
Cough	36 (8.9)	0	77 (19.4)	0
Mucosal inflammation	11 (2.7)	0	75 (18.9)	12 (3.0)
Nausea	57 (14.0)	1 (0.2)	66 (16.6)	3 (0.8)
Hypertriglyceridemia	5 (1.2)	0	64 (16.1)	20 (5.0)
Pneumonitis	16 (3.9)	6 (1.5)	58 (14.6)	11 (2.8)
Oedema peripheral	17 (4.2)	0	56 (14.1)	2 (0.5)
Pruritus	57 (14.0)	0	39 (9.8)	0
Dyspnoea	30 (7.4)	3 (0.7)	51 (12.8)	2 (0.5)
Hyperglycaemia	9 (2.2)	5 (1.2)	46 (11.6)	15 (3.8)
Epistaxis	3 (0.7)	0	41 (10.3)	0
Key: TRAEs, treatment-related adverse events. NICE technical team notes that the company's submission does not define how adverse events were designated treatment-				

related or not.

4.18 In CheckMate 025 there were no treatment-related deaths in the nivolumab group compared with 2 in the everolimus group. In CheckMate 025 a lower proportion of patients stopped nivolumab (8%) because of drug toxicity compared with those stopping everolimus (13%).

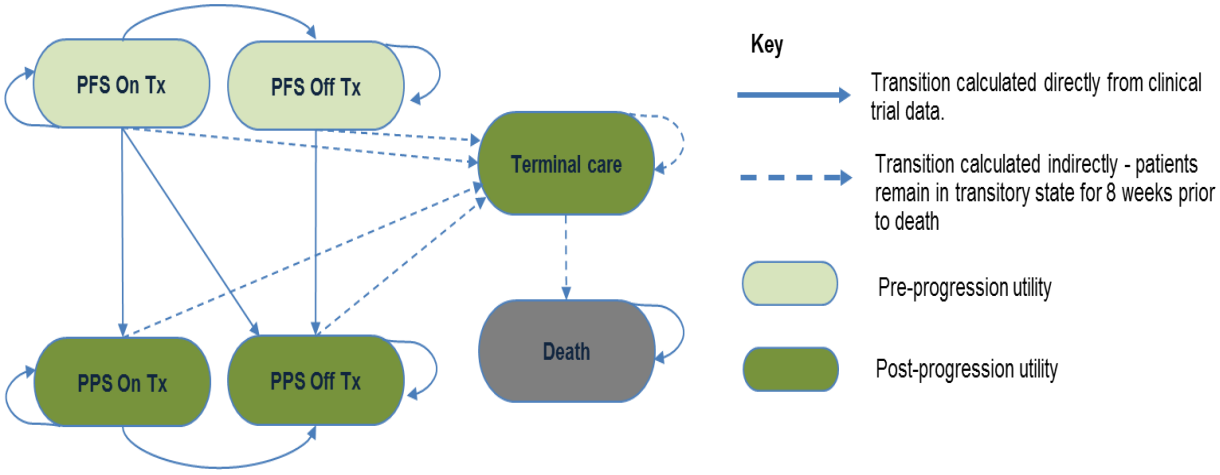
4.19 The company compared adverse events in the axitinib arm of the AXIS trial and the nivolumab arm of CheckMate 025. Based on 'qualitative synthesis' the company stated that there was a 'similar safety advantage' for nivolumab versus axitinib as was observed for nivolumab versus everolimus.

5 Cost-effectiveness evidence

Model structure

5.1 The company constructed a partitioned-survival (area under the curve) model comparing nivolumab with everolimus, axitinib and best supportive care (BSC). The model had 6 health states (see Figure 5) reflecting whether patients were having treatment, whether the disease had progressed, and whether patients were alive. The model included a 30-year time horizon, 1-week cycle length and discounting of costs and health benefits at 3.5% per year. The company included the costs incurred by the NHS and personal social services. The modelled population reflected the marketing authorisation; that is, adults with previously treated advanced renal cell carcinoma. The inputs to the model are summarised in table 59, section 5.6.1 of the company submission.

Figure 5 Structure of the company's economic model (figure 23, section 5.2.2 of company's submission)



PFS, progression-free survival; PPS, post-progression survival; Tx, treatment

ERG comments

5.2 The ERG noted that the structure of the model was appropriate. It identified errors relating to calculating the area-under-the-curve for overall survival, progression-free survival and time to discontinuation but these did not substantially affect the company's base case (see Table 11).

5.3 The NICE technical team was uncertain whether the model was intended to reflect second- or third-line use of nivolumab, or both. The efficacy estimates for nivolumab and everolimus came from the CheckMate 025 trial, in which 72% of patients had only 1 prior therapy and 28% had 2.

Model details

Clinical parameters

5.4 **For patients having nivolumab or everolimus**, the company calculated the time in each health state using parametric curves fitted to the CheckMate 025 data; it extrapolated the curves beyond the end of the trial.

- For overall survival, the company assumed proportional hazards and fitted a single model to the trial data with a predictor of treatment group.

The company stated that the log-logistic model gave the best statistical fit, but clinical experts thought the predicted survival times for everolimus were too optimistic. Instead, the company chose a generalised gamma distribution for its base case (see Figure 6).

- For progression-free survival, the company stated that the proportional hazards assumption did not hold so it fit independent models to each treatment group. The company decided that standard parametric models did not fit the data well, so in the base case it used a 'spline odds 2-knot' model (see Figure 7). NICE Technical Support Document 14 (survival analysis for economic evaluations alongside clinical trials) describes spline-based models as flexible parametric survival models that resemble generalised linear models with link functions.
- The company assumed that patients can continue treatment with nivolumab or everolimus after disease progression. The company assumed proportional hazards and fitted a single model to the trial data with a predictor of treatment group. It used a 'spline hazard 2-knot' model to predict time to stopping treatment (see Figure 8).

5.5 **For patients having axitinib or best supportive care**, the company took crossover-adjusted hazard ratios from the network meta-analysis and applied those hazard ratios to the curves predicting overall survival and PFS with everolimus (see Table 7). The company assumed that patients stop axitinib treatment when disease progresses.

Figure 6 Overall survival curves in the company's base case (generalised Gamma) (taken from figure 29 in section 5.3.1 of company's submission)

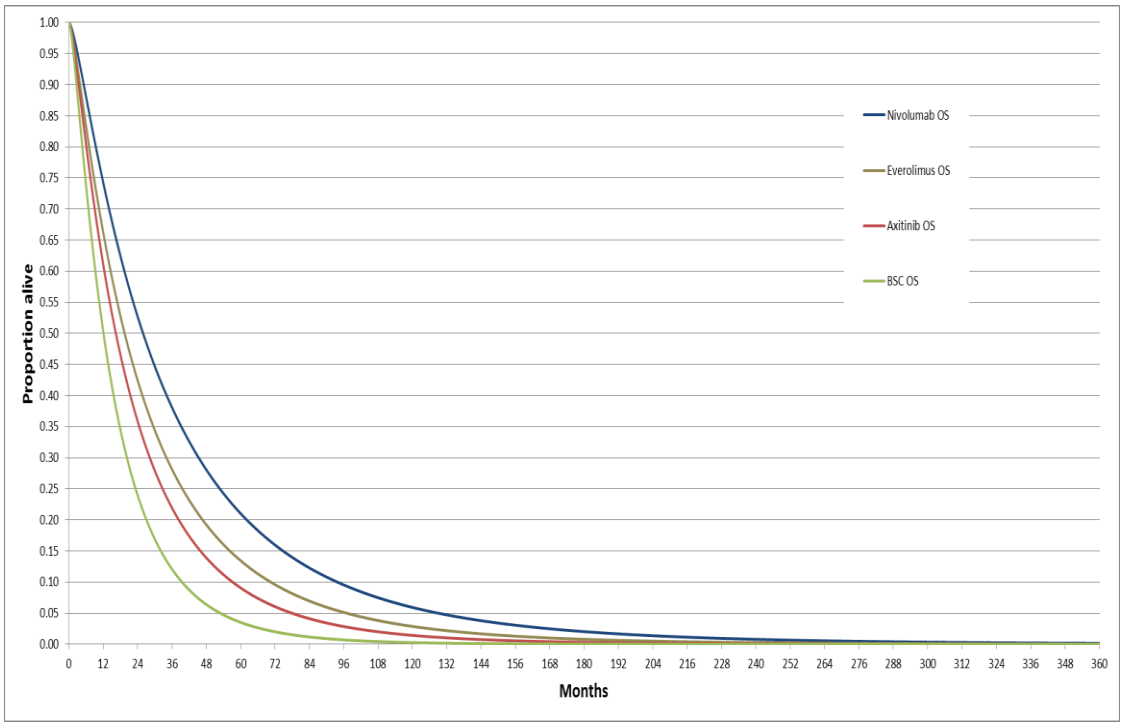


Figure 7 PFS curves in the company's base case (2-knot spline odds model) (taken from figure 38 in section 5.3.2 of company's submission)

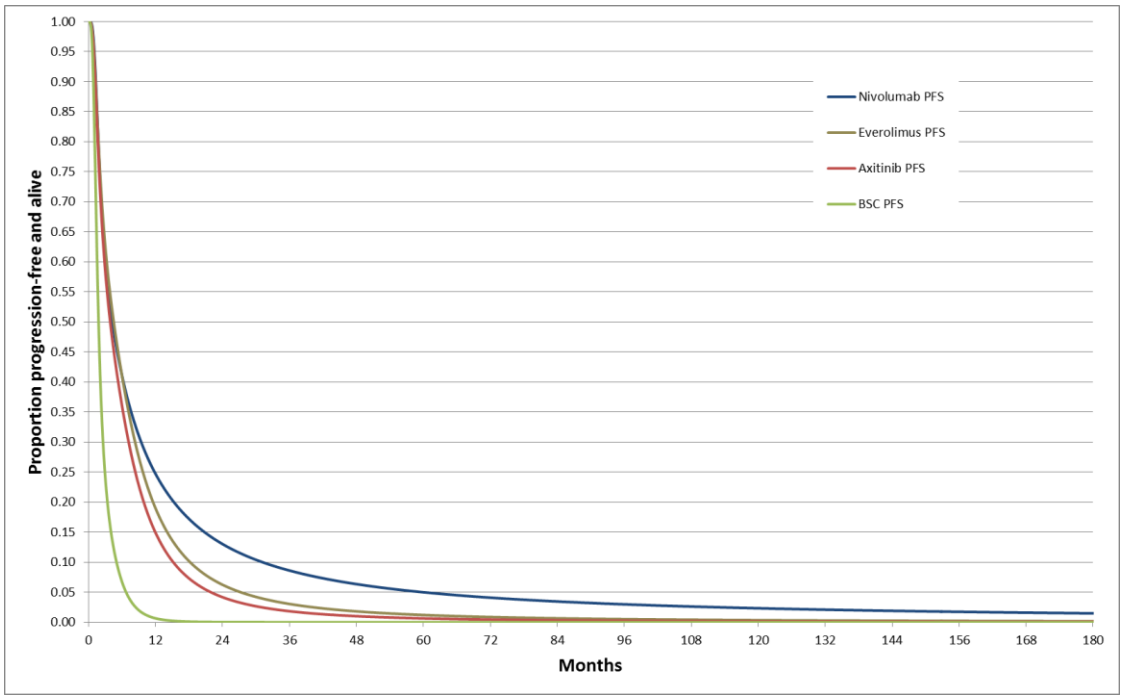


Figure 8 Time to stopping treatment curves in the company's base case (2-knot spline hazard model) (taken from figure 45 in section 5.3.3 of the company's submission)

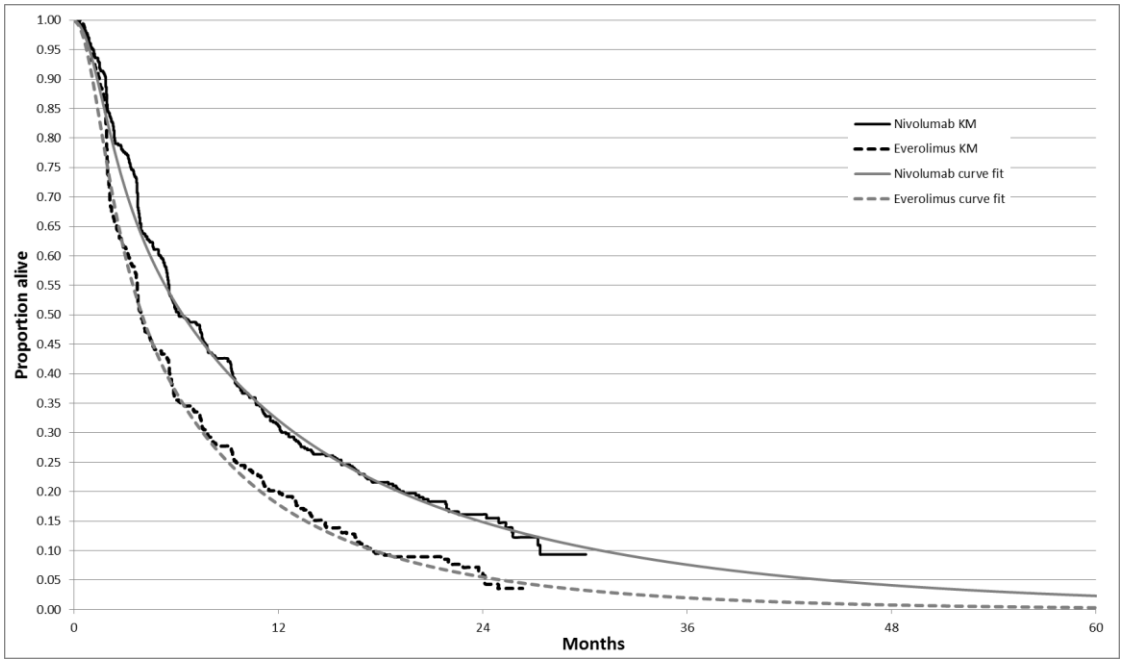


Table 7 Results of the company's network meta-analysis for everolimus versus axitinib and placebo (adapted from tables 29, 30 and 34 of ERG report)

	Intention-to-treat HR (95% credible interval) – used in scenario analyses	Crossover-adjusted HR (95% credible interval) – used in base case
Overall survival		
Everolimus vs axitinib	[redacted]	[redacted]
Everolimus vs placebo	[redacted]	[redacted]
Progression-free survival		
Everolimus vs axitinib	[redacted]	[redacted]
Everolimus vs placebo	[redacted]	[redacted]
HR, hazard ratio; NA, not applicable		

ERG comments

5.6 **Model population** The ERG noted that the company's method for estimating relative treatment effects and utility values assumed that the patient populations were similar in AXIS and CheckMate 025 (see sections 5.10–5.12). In the ERG's opinion these trial populations were different (see section 4.15).

5.7 **Overall survival model** The ERG considered that the log cumulative hazard plot for CheckMate 025 showed that the proportional hazards assumption was not met (see figure 25 in section 5.3.1 of the company submission). The company's experts advised that the best-fitting log-logistic model gave implausibly long survival times; the ERG commented that this may be because the patients in CheckMate 025 had a better prognosis than NHS patients.

5.8 **Time to stopping treatment** The ERG considered that the company did not justify its choice of a complex spline-based model. The ERG advised that a simpler model would also fit the data well. Accordingly, the ERG's exploratory analyses used a log-normal curve (base case) or a generalised gamma curve (sensitivity analyses).

5.9 **Relative treatment effectiveness between everolimus and axitinib** The model was informed by the company's network meta-analysis, which showed that axitinib is less effective than everolimus; the ERG advised that this is not plausible (see section 4.16). Accordingly, the model is likely to underestimate the effectiveness of axitinib. The ERG in its modelling chose to use the everolimus treatment group from CheckMate 025 as a surrogate to represent outcomes for patients treated with axitinib; this decision was based on clinical expert feedback and the non-significant difference between these 2 treatments in the company's network meta-analysis.

Health-related quality of life

5.10 Based on table 49 in section 5.4.4 of the company's submission, the NICE technical team inferred that the model utility values were the same regardless of whether patients were having treatment or not. Utility values decreased when patients moved from a pre-progression to a post-progression health state.

5.11 For patients treated with nivolumab or everolimus, the company calculated utility values using a regression model fit to EQ-5D utility data

from CheckMate 025. The base-case utility values were higher for patients treated with nivolumab than for patients treated with everolimus, both before and after disease progression (Table 8).

5.12 For patients treated with axitinib, the company took EQ-5D utility values from the AXIS study; these values were used in TA333. For the pre-progression health state, the company used the mean value for on-treatment utility. For the post-progression health state, the company used the mean utility at the time of stopping treatment. For patients having BSC, the company used the same utility values as for axitinib. The utility values for patients treated with axitinib or BSC were lower than those for patients treated with nivolumab or everolimus. The company presented 2 scenario analyses with different utility values for the comparators (see table 73 in section 5.8.3 of the company's submission).

5.13 In its base case, the company did not include the disutility associated with adverse events; it stated that the impact of adverse events would be captured by the EQ-5D data from the CheckMate 025 and AXIS trials. In a scenario analysis, the company included the disutility associated with 'treatment-emergent serious' grade 3 or 4 adverse events that occurred in at least 1% of patients in either treatment group of CheckMate 025 (pneumonitis, diarrhoea, anaemia and pneumonia).

Table 8 Utility values in the company's model (adapted from table 49 in section 5.4.4 of company's submission)

State	Utility value	Justification
Pre-progression, nivolumab	0.80	CheckMate 025 EQ-5D data
Post-progression, nivolumab	0.73	
Pre-progression, everolimus	0.76	
Post-progression, on treatment, everolimus	0.70	
Pre-progression, axitinib	0.69	AXIS EQ-5D data; TA333
Post-progression, axitinib	0.61	
Pre-progression, BSC	0.69	Assumption from TA333
Post-progression, BSC	0.61	
Pneumonitis	-0.15	Medical oncologist opinion

Diarrhoea	-0.1	and 'best available evidence'
Anaemia	-0.081	
Pneumonia	-0.13	

ERG comments

5.14 **Health state utility values** The model used lower utility values for BSC and axitinib than for nivolumab and everolimus. The ERG's clinical experts advised that this difference was probably due to differences in trial populations, rather than the treatment received. The clinical experts found it unreasonable that the quality of life of patients receiving everolimus with progressed disease exceeded those receiving axitinib who were progression-free. In its exploratory analysis, the ERG used the everolimus EQ-5D data from CheckMate 025 to inform the utility values for axitinib and BSC .

5.15 The lead team members of the appraisal committee noted that nivolumab is administered intravenously, and in other appraisals patient experts have advised that quality of life is higher for patients who take oral medication.

Resource use and costs

5.16 The company used the list price for nivolumab and it included the cost of intravenous administration. It assumed that patients took 92% of the licensed dose based on CheckMate 025. To estimate the number of vials needed, the company used the distribution of body weight among Western European patients in CheckMate 025 (mean 80.93 kg). It assumed there was no vial sharing (that is, any unused nivolumab left in the vial would be wasted).

5.17 The company used the list price for everolimus and axitinib. It assumed that patients took 94% of the licensed dose of everolimus (based on CheckMate 025) or 102% of the licensed dose of axitinib (based on the AXIS trial).

5.18 The company estimated the disease management costs associated with each health state (including visits from GPs and nurses, CT scans, blood

tests and pain medication). The company used the same resource use and unit cost estimates as in TA333, updated to 2014/15 costs. Costs were taken from NHS reference costs and the Personal Social Services Research Unit.

5.19 Although the company's base case did not explicitly include the disutility associated with adverse events, it did include the costs of treating serious grade 3 or 4 treatment-emergent adverse events that occurred in at least 1% of patients in either treatment group of CheckMate 025. The probability of each event was calculated using data from CheckMate 025 (for nivolumab and everolimus) and resource use was estimated using expert opinion. The cost of adverse events for axitinib patients was assumed to be equivalent to everolimus patients. The per-cycle cost of adverse events was £0.35 for nivolumab and £1.31 for both everolimus and axitinib.

5.20 The company included the costs of subsequent therapy after disease progression, based on the subsequent treatments used by CheckMate 025 patients (excluding bevacizumab which the company stated is not used in the NHS). The model included subsequent treatment with axitinib, everolimus, pazopanib, sorafenib or sunitinib; the distribution of treatments differed between model arms (see table 56 in section 5.5.5 of the company submission). The costs of subsequent treatment after axitinib were assumed to be the same as the costs after everolimus.

5.21 The model included a cost of £6,160 for 8 weeks of end-of-life care, based on a King's Fund report. For further details of model costs see section 5.5 of the company's submission.

ERG comments

5.22 **Proportion of planned drug received** The company deducted the cost of delayed doses for nivolumab; the ERG advised that this may be inappropriate if those doses are eventually received. The ERG also queried the assumption that the dose reduction applied to nivolumab and

everolimus was constant over time. In a scenario analysis, the ERG assumed that patients have 100% of planned nivolumab and everolimus doses.

5.23 **Subsequent therapy costs** The ERG noted that subsequent therapy after a second treatment is not recommended by NICE. According to the ERG's experts, subsequent therapy is not offered in clinical practice and is not expected to provide a clinical benefit. The ERG removed the costs of subsequent therapy in its exploratory analysis.

Company's base-case results and sensitivity analysis

5.24 The company presented its results as pairwise comparisons between nivolumab and each comparator (table 6). Using list prices for all treatments, the company's deterministic base case showed that nivolumab compared with axitinib resulted in an incremental cost-effectiveness ratio (ICER) of £42,417 per QALY gained. Comparing nivolumab with everolimus the ICER was £83,829 per QALY gained, and comparing nivolumab with BSC the ICER was £56,427 per QALY gained.

5.25 The company's one-way sensitivity analysis showed that the main driver of the results was the hazard ratio comparing overall survival with everolimus and axitinib. The probabilistic sensitivity analysis showed that the probability of nivolumab being cost effective compared with axitinib at a threshold of £50,000 per QALY gained was 0.608.

Table 9 Company's pairwise base case results (adapted from tables 60 and 72 in sections 5.7.1 and 5.8.1 of company's submission)

			Increments nivolumab vs each comparator		
Treatment	**Total costs (list price)**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
Deterministic results					
Nivolumab	£91,353	2.31			
Axitinib	£46,134	1.25	£45,219	1.07	£42,417
Everolimus	£38,920	1.69	£52,432	0.63	£83,829
BSC	£10,525	0.88	£80,828	1.43	£56,427
Probabilistic results					

Nivolumab	£91,964	2.36			
Axitinib	£48,655	1.46	£43,310	0.90	£47,928
Everolimus	£39,127	1.72	£52,838	0.64	£82,288
BSC	£11,270	1.02	£80,694	1.34	£60,077
Abbreviations: BSC, best supportive care; Inc., incremental; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio					

Table 10 Company's deterministic fully incremental analysis (adapted from the economic model)

			Increments nivolumab vs each comparator		
Treatment	**Total costs (list price)**	**Total QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
BSC	£10,525	0.88			
Everolimus	£38,920	1.69	£28,395	0.81	£35,188
Axitinib	£46,134	1.25	£7,213	-0.44	Dominated
Nivolumab	£91,353	2.31	£52,432	0.63	£83,829
Abbreviations: BSC, best supportive care; Inc., incremental; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio					

ERG corrections

5.26 The ERG identified errors in the model's calculation of overall survival, PFS, time to stopping treatment, and costs. Table 8 shows the deterministic results with the errors corrected; the ICERs increased slightly compared with the company's base case. The ERG presented the results of the company's model when using the confidential patient access scheme discount for axitinib (see the confidential appendix to this pre-meeting briefing).

Table 11 ERG's revised version of the company's base case with model errors corrected (see table 62 in section 6.1 of the ERG report).

			Increments nivolumab vs each comparator		
Treatment	**Total costs (list price)**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
Nivolumab	£91,326	2.30			
Axitinib	£46,113	1.25	£45,213	1.04	£43,109
Everolimus	£38,933	1.69	£52,393	0.61	£86,136
BSC	£10,525	0.88	£80,801	1.42	£57,096
Abbreviations: BSC, best supportive care; Inc., incremental; QALY, quality adjusted life year;					

ICER, incremental cost effectiveness ratio

ERG exploratory analyses

5.27 The ERG's preferred base case:

- assumed axitinib was as effective as everolimus for PFS and overall survival (see 5.9); this increased the ICER for nivolumab compared with axitinib
- used a log-normal distribution to predict time to stopping treatment (see 5.8); this decreased all ICERs for nivolumab
- assumed patients receive all planned doses of nivolumab and everolimus (see 5.22); this increased all ICERs for nivolumab
- took utility values for axitinib and BSC from the everolimus group in CheckMate 025 (see 5.14); this increased the ICERs for nivolumab compared with axitinib and BSC
- removed subsequent therapy costs (see 5.23); this increased the ICERs for nivolumab compared with axitinib and everolimus and decreased the ICER for nivolumab compared with BSC.

The impact of each change is shown using pairwise ICERs in Table 12; the ERG's fully incremental analysis is in Table 13.

Table 12 ERG exploratory analyses, presented as pairwise comparisons with nivolumab (adapted from tables 63 and 64 in section 6.2 of the ERG's report)

Scenario	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
ERG's corrected version of company base case					
Nivolumab	£91,326	2.30			
Axitinib	£46,113	1.25	£45,213	1.05	**£43,109**
Everolimus	£38,933	1.69	£52,393	0.61	**£86,136**
BSC	£10,525	0.88	£80,801	1.42	**£57,096**
A) Assume axitinib as effective as everolimus for PFS and overall survival					
Nivolumab	£91,326	2.30			
Axitinib	£52,683	1.49	£38,643	0.80	**£48,218**
Everolimus	£38,933	1.69	£52,393	0.61	**£86,136**
BSC	£10,525	0.88	£80.801	1.42	**£57,096**
B) Log-normal distribution for time to stopping treatment (single model with a					

predictor of treatment group)					
Nivolumab	£90,791	2.30			
Axitinib	£52,683	1.49	£38,108	0.80	**£42,599**
Everolimus	£40,659	1.69	£50,132	0.61	**£82,419**
BSC	£10,525	0.88	£80,266	1.42	**£56,718**
C) Assume patients receive all planned doses of nivolumab and everolimus					
Nivolumab	£96,292	2.30			
Axitinib	£52,707	1.49	£43,585	0.80	**£48,375**
Everolimus	£41,917	1.69	£54,375	0.61	**£93,384**
BSC	£10,525	0.88	£85,767	1.42	**£61,016**
D) Utility values for axitinib and BSC equal to everolimus group in CheckMate 025					
Nivolumab	£96,292	2.30			
Axitinib	£52,707	1.69	£43,585	0.61	**£50,946**
Everolimus	£41,917	1.69	£54,375	0.61	**£86,136**
BSC	£10,525	1.00	£85,767	1.30	**£62,379**
E) Remove subsequent therapy costs					
Nivolumab	£89.951	2.30			
Axitinib	£44,859	1.69	£45,092	0.61	**£44,798**
Everolimus	£33,997	1.69	£55,954	0.61	**£89,421**
BSC	£10,525	1.00	£79,426	1.30	**£52,760**
ERG's preferred base case (A + B + C + D + E)					
Nivolumab	£89,951	2.30			
Axitinib	£44,859	1.69	NR	NR	**£74,132**
Everolimus	£33,997	1.69	NR	NR	**£91,989**
BSC	£10,525	1.00	NR	NR	**£61,317**
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; NR, not reported					

Table 13 ERG's preferred base case, fully incremental analysis (adapted from table 65 in section 6.3 of ERG's report)

Comparator	Total costs (list price)	Total QALYs	Inc. costs	Inc. QALYs	ICER
BSC	£10,525	1.00			
Everolimus	£33,997	1.69	£23,472	0.69	£34,163
Axitinib	£44,859	1.69	£10,862	0.00	Absolutely dominated
Nivolumab	£89,951	2.30	£55,954	0.61	£91,989
Abbreviations: BSC, best supportive care; Inc., incremental; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio					

5.28 The ERG advised that a generalised gamma distribution for predicting time to stopping treatment gave an equally good fit as the log-normal

distribution used in its preferred base case. Using the generalised gamma distribution, and including all of the other changes in the ERG's preferred base case, raised the ICER for nivolumab compared with everolimus to £96,107 per QALY gained (see table 66 in section 6.3 of the ERG report).

Innovation

5.29 The company considers nivolumab to be innovative and represent a 'step-change' in managing advanced renal cell carcinoma (see section 2.5 of the company's submission):

- nivolumab is the first checkpoint inhibitor immunotherapy to gain a marketing authorisation in advanced renal cell carcinoma
- it provides an innovative mechanism of action that uses the body's own immune system to destroy cancer cells
- nivolumab was the first immunotherapy available for patients with advanced renal cell carcinoma after prior therapy through the Early Access to Medicines Scheme
- it is the first therapy to demonstrate a survival benefit for these patients compared with everolimus.

6 End-of-life considerations

Table 14 End-of-life considerations (see section 4.13, page 130-1, of the company's submission and section 7 of the ERG report)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In CheckMate 025, median survival with everolimus was 19.6 months. Mean survival was not reported. The company stated that median life expectancy is: • Less than 12 months with best supportive care (based on population studies and regulatory trial data) • About 20 months with axitinib (based on population studies and regulatory trial data).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of	In CheckMate 025, median survival was 5.4 months longer for patients randomised to nivolumab than for patients randomised to everolimus. The company's network meta-analysis showed that:

at least an additional 3 months, compared with current NHS treatment	• the survival benefit of nivolumab versus axitinib was not statistically significant (see Table 5). • the survival benefit of nivolumab versus best supportive care was statistically significant in the intention-to-treat analysis, but not when adjusting for crossover (see Table 5). Using the company's base-case model, the mean gain in life years was: • 1.4 years for nivolumab versus axitinib • 0.9 years for nivolumab versus everolimus • 2.0 years for nivolumab versus best supportive care Source: ERG report table 55.

7 Equality issues

7.1 No equality issues were identified during scoping and none were raised by consultees.

8 Authors

Anna Brett

Technical Lead

Rosie Lovett

Technical Adviser

with input from the Lead Team (Amanda Adler, Anne Joshua, Nigel Westwood and Stephen Palmer).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for previously treated advanced or metastatic renal cell carcinoma.

Background

Renal cell cancer (RCC) refers to cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (approximately 90% of the cases)[1]. There are several different types of RCC, with the main ones divided into 5 categories: clear cell, papillary (Types 1 and 2), chromophobe, oncocytic and collecting duct carcinoma. Clear cell is the most common form of RCC accounting for approximately 80–90% of cases.[2]

The tumour node metastases system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV.

Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other indications. The most common presenting symptoms of metastatic and/or advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. Nephron sparing surgery may be curative in people with localised tumours. However, around half of those who have curative resection for earlier stages of the disease also go on to develop advanced and/or metastatic disease later on.

In 2012, 8638 new kidney cancer cases were diagnosed in England.[3] In 2013, approximately 46% of people diagnosed with kidney cancer had stage III or IV disease and 27% had stage IV disease.[3] The 5-year survival rate for metastatic RCC is approximately 10%.[4]

The aim of treatment is to stop the growth of new blood vessels within a tumour. After failure of prior systemic treatment with a tyrosine kinase inhibitor or cytokine, NICE technology appraisal guidance 333 recommends axitinib. Because the remit referred to NICE by the Department of Health for axitinib only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding. This recommendation will be reviewed within the ongoing multiple technology appraisal of 'axitinib, everolimus, sorafenib and sunitinib for previously treated advanced or metastatic RCC'. Everolimus, sorafenib and sunitinib are not recommended after initial therapies had failed in NICE guidance (NICE technology appraisal guidance 178 and 219); however, everolimus is available in England for metastatic RCC through the Cancer Drugs Fund for some patients. The recommendations in technology appraisal guidance 219, and those in technology appraisal 178 on sorafenib and sunitinib for previously treated advanced or metastatic RCC, will also be reviewed within the ongoing multiple technology appraisal.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully human IgG4 monoclonal antibody which targets and blocks the programmed cell death-1 receptor (PDCD-1/PD-1), to promote an anti-tumour immune response. It is administered intravenously.

Nivolumab does not currently have a marketing authorisation in the UK for previously treated advanced or metastatic renal cell carcinoma. It has been studied in a clinical trial compared with everolimus, in adults with advanced or metastatic clear-cell RCC who have received at least 1 (but no more than 3) prior anti-angiogenic therapies, and have evidence of disease progression.

Intervention(s)	Nivolumab
Population(s)	People with previously treated advanced or metastatic renal cell carcinoma.
Comparators	• Axitinib • Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) • Best supportive care

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • previous treatment • prognostic score (for example, ECOG or Motzer). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment' (2015). NICE Technology Appraisal 333. 'Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE Technology Appraisal 178. 'Everolimus for the second-line treatment of advanced renal cell carcinoma' (2011). NICE Technology appraisal

	219. 'Pazopanib for the first-line treatment of advanced renal cell carcinoma' (2011). NICE Technology appraisal 215. Review date tbc. 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE Technology appraisal 169. On static list. Appraisals in development 'Axitinib, everolimus, sorafenib and sunitinib for previously treated advanced or metastatic renal cell carcinoma (incl. review of TA333 and TA219, and part review of TA178)'. NICE technology appraisals guidance [ID897]. Publication expected April 2017. Pazopanib for the second line treatment of metastatic renal cell carcinoma (discontinued)' NICE technology appraisals guidance [ID70]. Related Guidelines: 'Referral guidelines for suspected cancer' (2005). NICE guideline CG27. Review date June 2015. 'Improving outcomes in urological cancers (2002). NICE Guideline CSGUC. Review date tbc. Related Interventional Procedures: 'Irreversible electroporation for treating renal cancer (2013). NICE Interventional Procedure 443. 'Laparoscopic cryotherapy for renal cancer' (2011). NICE Interventional Procedure 405. 'Percutaneous cryotherapy for renal cancer' (2011). NICE Interventional Procedure 402. 'Percutaneous radiofrequency ablation for renal cancer' (2010). NICE Interventional Procedure 353. Related NICE Pathways: Renal Cancer (2015) NICE pathway

Related National Policy	NHS England (January 2014) Manual for prescribed specialised services. Section 105 (p236) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England: B14. Specialised Urology. NHS Care and Clinical Reference Groups. Link accessed: 26th February 2015 http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b14/ Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf Department of Health (2014) The national cancer strategy: 4th annual report https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report

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2. Patient.co.uk – Renal Cancer. Accessed January 2016
3. Cancer Research UK (2011) Kidney cancer incidence statistics. Accessed January 2016
4. GP Notebook - Clear Cell Cancer Accessed January 2016

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating advanced or metastatic renal cell carcinoma after anti-angiogenic therapy [ID853]

Provisional matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Bristol-Myers Squibb (nivolumab) Patient/carer groups • Black Health Agency • British Kidney Patient Association • Cancer Black Care • Cancer Equality • Cancer 52 • Helen Rollason Cancer Charity • HAWC • Independent Cancer Patients Voice • James Whale Fund for Kidney Cancer • Kidney Cancer Support Network • Kidney Cancer UK • Kidney Research UK • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • National Kidney Federation • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Association of Urological Nurses • British Association of Urological Surgeons • British Geriatrics Society • British Psychosocial Oncology Society • British Renal Society • Cancer Research UK	General • Allied Health Professionals Federation • Association of Renal Industries • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Kidney Patients Association • Welsh Urological Society Possible comparator companies • Pfizer (axitinib) • Novartis Pharmaceuticals (everolimus) Relevant research groups • Cochrane Prostatic Diseases and Urologic Cancers Group • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • The Institute of Cancer Research Associated Public Health Groups • Public Health England

Consultees	**Commentators (no right to submit or appeal)**
• Renal Association • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for DGH Nephrologists • The Urology Foundation • UK Clinical Pharmacy Association • UK Health Forum • UK Renal Pharmacy Group • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS City and Hackney CCG • NHS England • NHS Newham CCG • Welsh Government	• Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland;; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

Company evidence submission

Bristol Myers Squibb Pharmaceuticals Ltd.

March 2016

File name	Version	Contains confidential information	Date
ID853_Nivo Renal_NICE Submission_Final.docx	**1.0**	**Yes/~~no~~**	**02.03.2016**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology-Genitourinary
BIC	Bayesian Information Criterion
BMS	Bristol-Myers Squibb Pharmaceuticals Ltd
BNF	British National Formulary
BSC	Best supportive care
CDF	Cancer Drugs Fund
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CSR	Clinical study report
CT	Computerised tomography
CTC	Common terminology criteria
DC	Discontinuation
DMC	Data monitoring committee
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOL	End of life
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FKSI-15	15 item Functional Assessment of Cancer Therapy Kidney Symptom Index
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms
GCP	Good clinical practice
GI	Gastrointestinal

GP	General practitioner
HCHS	Hospital & community health services
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
INB	Incremental net benefit
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier
LLN	Lower limit of normal
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MSKCC	Memorial Sloane Kettering Cancer Centre
mTOR	Mammalian target of rapamycin
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-Small Cell Lung Cancer
ONS	Office of National Statistics
OP	Outpatient
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
OWSA	One-way sensitivity analysis
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand 1
PD-L2	Programmed death receptor ligand 2
PFS	Progression-free survival
PH	Proportional hazards
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life-year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
SAE	Serious adverse event
SD	Standard deviation
SGA LoT	Subgroup analysis for line of therapy
SNP	Single nucleotide polymorphisms
SmPC	Summary of Product Characteristics
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
TTP	Time-to-progression
Tx	Treatment
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau
WTP	Willingness-to-pay

1 Executive summary

Renal cell carcinoma (RCC) accounts for over 80% of all cases of kidney cancer and is the seventh most common cancer in the UK. Like many other solid malignancies, if detected at an early (localised) stage, RCC is potentially curable with surgical resection. However, approximately 30% of all patients diagnosed with RCC will present with advanced disease where the cancer has grown into the tissues around the kidney or spread to other parts of the body (advanced RCC). The predicted incidence of advanced RCC in England for 2016 is approximately 2,500; these patients have a particularly poor outlook with 5-year survival rates of 10-15%.

Advanced RCC impacts on all domains of health-related quality of life (HRQL) including physical and psychosocial function. In addition to patient burden, advanced RCC can also present a significant burden to informal caregivers and the wider society, primarily as a result of direct care requirements and reduced life expectancy; as both are worsened with disease progression. In consideration of the ageing population and the rising prevalence of risk factors such as obesity, particularly in industrialised countries, the incidence of advanced RCC and thus the burden of this disease are increasing worldwide.

There is no cure for advanced RCC; therefore, treatment goals are to extend life and delay disease progression while relieving physical symptoms and maintaining physical function. Considerable advancements in RCC therapeutics have been made over the last decade with the introduction of targeted therapy (including vascular endothelial growth factor receptor [VEGFR] tyrosine-kinase inhibitor [TKI] and mammalian target of rapamycin [mTOR] inhibitor agents), which demonstrates significant clinical benefit over traditional treatments (e.g. chemotherapy and cytokines). However, limitations with available targeted agents mean that treatment goals are still not being met for many patients with advanced RCC, particularly those who demonstrate progressive disease despite receiving active treatment.

Standard of care for patients with advanced RCC in England typically consists of the sequencing of VEGFR TKI's for first and subsequent lines of therapy. This is the only class of targeted therapy routinely recommended by NICE. For patients who fail first-line therapy, active treatment options include axitinib (a VEGFR TKI) or everolimus (an mTOR inhibitor) which is available through the Cancer Drugs Fund (CDF) under

specific circumstances. Neither axitinib nor everolimus are associated with a proven overall survival (OS) advantage, and the life-expectancy for patients with advanced RCC who have received prior therapy still does not typically exceed 2 years. Furthermore, these treatments can be associated with toxicity profiles that may counteract positive benefit from clinical efficacy (extended time to disease progression) on the patient's quality of life. There is a clear and substantial unmet medical need for additional treatment options in advanced RCC, specifically, a more tolerable treatment option with proven OS and HRQL benefit for patients with advanced RCC who have received prior therapy. Nivolumab meets this unmet need.

Nivolumab is the first therapy to demonstrate a significant OS benefit in patients with advanced RCC who have received prior therapy in a Phase III trial setting. In the pivotal regulatory trial, CheckMate 025, nivolumab significantly improved median OS by over 5 months compared with the targeted therapy, everolimus (hazard ratio [HR] for death: 0.73). Modelled survival estimates from the network meta-analysis (NMA) suggest a superior OS benefit of nivolumab over axitinib and BSC, to that observed over everolimus. Moreover, the potential for longer-term survival is supported with Phase I/II trial data that report 3-year survival rates of up to 44% and an unprecedented 5-year survival rate of 34%. In addition to this survival benefit, nivolumab resulted in constant improvement in disease-specific patient HRQL (assessed with the use of the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms [FKSI-DRS] scoring algorithm) in CheckMate 025, and HRQL improvement was significantly greater than that observed in patients treated with everolimus at each assessment point from study entry through to Week 104 ($p<0.05$). Importantly, nivolumab also demonstrates a favourable safety profile compared with targeted therapy.

Further to this compelling trial data, nivolumab is the first monoclonal antibody immunotherapy drug to file for marketing authorisation in advanced RCC and after a positive scientific opinion by the Medicines and Healthcare products Regulatory Agency (MHRA) is the first immunotherapy available for patients with advanced RCC after prior therapy through an Early Access to Medicines Scheme (EAMS). Nivolumab offers an interruption to the standard VEGFR TKI - VEGFR TKI sequencing which could reduce the risk of resistance and excessive overlap of similar side-effects between first- and subsequent-line treatments. In consideration of

its favourable safety profile, nivolumab may also offer an active treatment option for some patients unable to tolerate further targeted therapy, as well as offering an active treatment option for patients who have exhausted all treatment options available in current practice.

With a median life expectancy of less than 24 months for patients with advanced RCC who have received prior therapy; a median extension to life of over 5 months associated with nivolumab (compared to targeted therapy with everolimus); and a small patient population potentially eligible for nivolumab in England (estimation of n=1,823 in year 1), nivolumab for the treatment of patients with advanced RCC who have received prior therapy meets NICE's end of life criteria.

Taking everything into consideration, nivolumab offers a step-change in the management of advanced RCC. Indeed, the potential of nivolumab to change treatment paradigms for patients with advanced RCC has recently been acknowledged by the European Association of Urology who released an update to their guidelines, recommending nivolumab as a second-line treatment option with an OS advantage. The adoption of nivolumab for the treatment of patients with advanced RCC who have received prior therapy in the National Health Service (NHS) in England would therefore represent a further, significant advance in the management of this life-threating condition.

1.1 Statement of the decision problem

The decision problem addressed in this submission matches that described in the final scope, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated advanced or metastatic renal cell carcinoma	People with previously treated advanced or metastatic renal cell carcinoma	-
Intervention	Nivolumab	Nivolumab	-
Comparator(s)	Axitinib Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) Best supportive care	Axitinib Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) Best supportive care	Axitinib is the most relevant comparator for nivolumab in English clinical practice and is therefore presented as the key comparison in this submission. Comparisons to everolimus and best supportive care are also included in accordance with the specified scope of the decision problem
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 30 years is used in the base case analysis.	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	Costs are considered from a National Health Service and Personal Social Services perspective. List prices are used within the submission document as requested by NICE.	
Subgroups to be considered	None specified.	None specified.	-
Special considerations including issues related to equity or equality	If the evidence allows the following subgroups will be considered. These include: Previous treatment Prognostic score (for example, ECOG or Motzer) Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing	None identified	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	authorisation granted by the regulator.		

1.2 Description of the technology being appraised

Programmed death-1 (PD-1) is an immune-system checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy. Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Nivolumab stops the evasion of immune-mediated tumour destruction and stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes.

The indication for nivolumab of interest to this appraisal is as follows:

Opdivo® as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Details of the technology being appraised in this submission are summarised in Table 2.

Table 2: Technology being appraised

UK approved name	Nivolumab
Brand name	Opdivo®
Marketing authorisation status	Marketing authorisation application filed to the EMA in October 2015 CHMP positive opinion received 25 February 2016 Marketing authorisation anticipated April 2016
Indications and any restriction(s) as described in the summary of product characteristics	Opdivo® as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.
Method of administration and dosage	Nivolumab 3mg/kg every 2 weeks by intravenous infusion. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Key: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; RCC, renal cell carcinoma.	

1.3 Summary of the clinical effectiveness analysis

A comprehensive clinical trial programme supports the use of nivolumab for the treatment of patients with advanced RCC who have received prior therapy.

This clinical trial programme includes a pivotal Phase III randomised controlled trial (RCT) that provides direct evidence of the potential clinical effectiveness of nivolumab compared with a targeted therapy. A summary of this trial is provided below:

CheckMate 025

- Phase III, multicentre, open-label RCT comparing the clinical efficacy and safety of nivolumab with everolimus (a standard therapy at the time of trial initiation) in adult patients with advanced RCC who had received one or two previous regimens of antiangiogenic therapy, representative of current UK practice.

- Significant benefit with respect to the primary endpoint of OS was observed in the nivolumab group (median OS, 25.0 months), compared with the everolimus group (median OS, 19.6 months): hazard ratio (HR) for death, 0.73 (98.5% confidence interval [CI]: 0.57, 0.93); p=0.0018.
- OS benefit was observed irrespective of patient characteristics and baseline prognosis, including in pre-specified subgroup analyses based on PD-L1 tumour expression status, previous treatment and prognostic score.
- Median progression-free survival (PFS) between the two arms (nivolumab: 4.6 months [95% CI, 3.7 to 5.4], everolimus: 4.4 months [95% CI, 3.7 to 5.5]) was not statistically significant (HR, 0.88; 95% CI, 0.75 to 1.03; p= 0.11). However ad-hoc sensitivity analysis of those patients that did not progress or die within 6 months of study entry, yielded a median PFS of 15.6 months (95% CI, 11.8 to 19.6) with nivolumab versus 11.7 months (95% CI, 10.9 to 14.7) with everolimus (HR 0.64; 95% CI, 0.47 to 0.88).
- Significant benefit with respect to the secondary endpoint of ORR was observed in the nivolumab group (25.1%), compared with the everolimus group (5.4%): odds ratio (OR) for response, 5.98 (95% CI: 3.68, 9.72); p<0.001.
- Potential durability of clinical response to nivolumab was demonstrated by 31% of responders (32 of 103) continuing to respond to treatment for 12 months or more. In patients with confirmed objective response (n=104), median duration of response was [redacted] months in the nivolumab group compared with [redacted] months in the everolimus group.
- Significant benefit with respect to the secondary endpoint of disease specific HRQL (FKSI-DRS) was observed in the nivolumab group with constant improvement reported throughout treatment which was significantly greater than that observed in the everolimus group at each assessment point from study entry through to week 104; p<0.05.

With a minimum follow-up of 14 months, only the 1-year survival rate associated with nivolumab can be estimated based on CheckMate 025 data ([redacted]). The potential for longer-term survival is supported by Phase I/II data from the CheckMate 003 and CheckMate 010 trials that demonstrate 3-year survival rates of 33-44% in patients with advanced RCC who have received prior therapy, depending on nivolumab dose used; CheckMate 003 has also recently reported an unprecedented 5-year survival rate of 34%. Durability of clinical response with nivolumab in at least a proportion of patients is also supported with these data. The Phase II trial reports ongoing responses of at least 2 years duration in approximately 40% of responders (14 of 35). In CheckMate 003, where treatment was of fixed duration (up to 96 weeks), 30% of responders (3 of 10) had persistent response (approximately 1 year) post treatment discontinuation.

In the absence of head-to-head data outside of CheckMate 025, the OS benefit of nivolumab versus additional comparators has been estimated using a NMA approach. Modelled estimates suggest that nivolumab offers a superior survival benefit compared with axitinib and BSC similar to that observed over everolimus: HR for death versus axitinib, 0.61 (95% CI: 0.21, 1.82); HR for death versus BSC, 0.44 (95% CI: 0.16, 1.22). As with all indirect estimates, there is uncertainty associated with these analyses but the approach taken was designed to minimise uncertainty, despite a paucity of data available and heterogeneity across trials and all sensitivity analyses support trends observed in the base case analysis.

Common side effects associated with nivolumab are reflective of its therapeutic class and will be familiar to clinicians using immunotherapy agents in other indications. Immune select adverse events (AEs) that do occur are predictable and medically manageable with established safety algorithms in the majority of cases. In CheckMate 025, reduced rates of treatment-related AEs (79% versus 88%; Grade 3-4: 19% versus 37%), dose delays (51% versus 66%) and discontinuations due to treatment-related AEs (8% versus 13%) clearly demonstrate a more favourable safety and tolerability profile of nivolumab, compared with everolimus. Importantly, no deaths related to study-drug toxicity were reported across trials of nivolumab in

advanced RCC. Qualitative synthesis of common AEs observed with targeted therapy suggest a similar safety advantage with nivolumab compared with axitinib.

Taken together, the clinical data from these trials present a compelling case that nivolumab represents a significant advance in the treatment of advanced RCC, offering a survival and HRQL benefit as well as reduced toxicity to patients who have received prior therapy.

1.4 Summary of the cost-effectiveness analysis

To appraise nivolumab for previously treated RCC patients, a de novo economic model was developed. A six-state Markov model structure was used, based upon previously accepted economic models in advanced, previously treated RCC, and to capture the key clinical outcomes of time to treatment discontinuation, progression-free survival (PFS) and OS. Clinical data from the pivotal CheckMate 025 trial were used to inform clinical effectiveness estimates for nivolumab and everolimus; a network meta-analysis was used to extend the analysis to compare to axitinib and BSC. HRQL assumptions were informed by EQ-5D data from CheckMate 025, and patient-reported EQ-5D data from the most recent appraisal in previously treated RCC patients (TA333).

The structure and assumptions of the economic model were validated by oncologists practicing in the NHS and with experience of nivolumab and its comparators. Model estimates of PFS and OS are comparable to clinical data and broadly consistent with clinical expectations, with the exception of OS for nivolumab patients, for which an immune-response tail was expected, but not assumed for the base case model extrapolations.

Nivolumab is predicted to be a highly effective and cost-effective end-of-life treatment option for advanced, relapsed RCC patients, versus axitinib, the only recommended active treatment in this indication. The base case analysis predicts patients treated with nivolumab will experience a survival benefit of 1.35 years (1.07 QALYs) versus axitinib. The base case incremental cost-effectiveness ratio for

nivolumab versus axitinib is less than £42,500 per QALY gained, representing good value for money to the NHS and a step-change improvement in care for patients.

2 The technology

2.1 Description of the technology

Brand name: Opdivo®

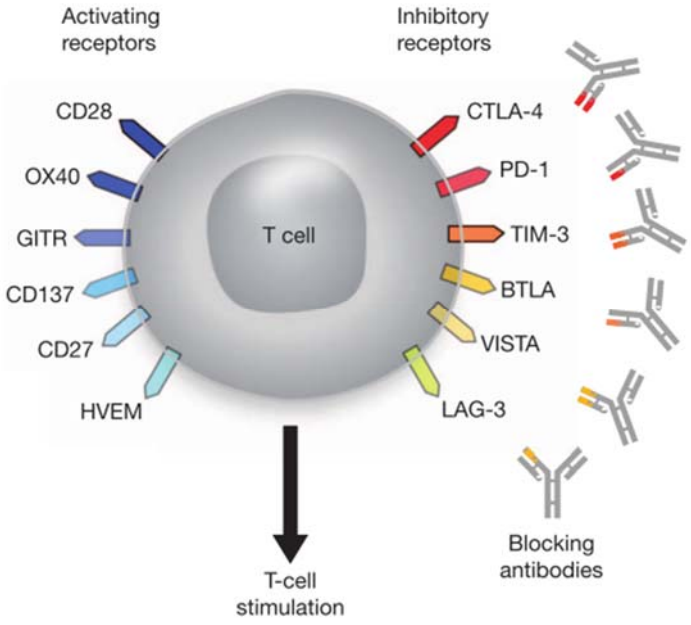
UK approved name: Nivolumab

Therapeutic class: Programmed death-1 (PD-1) immune checkpoint inhibitor

Brief overview of the mechanism of action:

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting the signalling pathways that control the immune system. The typical immune response to foreign cells or antigens in the body is the activation of T-cells that can then destroy those foreign cells or antigens. T-cells proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by co-stimulatory and co-inhibitory receptor interactions on the T-cell surface (Figure 1). Healthy, non-foreign cells ('self'-cells) avoid T-cell destruction by stimulating inhibitory receptors, known as checkpoints, to suppress the T-cell response; cancer cells can use these same inhibitory receptors to escape destruction by T-cell activity. Blocking antibodies designed to bind to these checkpoints (so called 'checkpoint-inhibitors') can prevent tumour driven T-cell suppression, as depicted in Figure 1, and increase immune activity against cancer cells.

Figure 1: Receptors involved in the regulation of the T-cell immune response

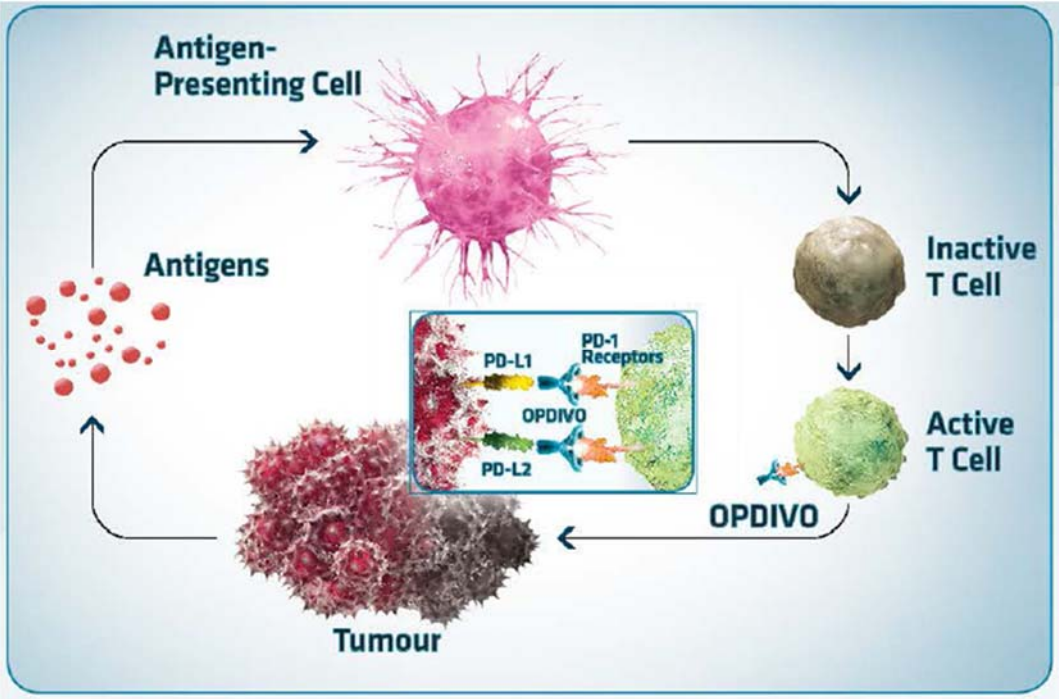


Source: Mellman et al., 2011[1]

PD-1 is an immune checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy.[2, 3]. Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2, as depicted in Figure 2.[4, 5] Nivolumab stops the evasion of immune-mediated tumour destruction and actually potentiates this process by restoring T-cell activity; that is, nivolumab stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes (Figure 2).

Figure 2: Nivolumab stimulation of immune-mediation destruction

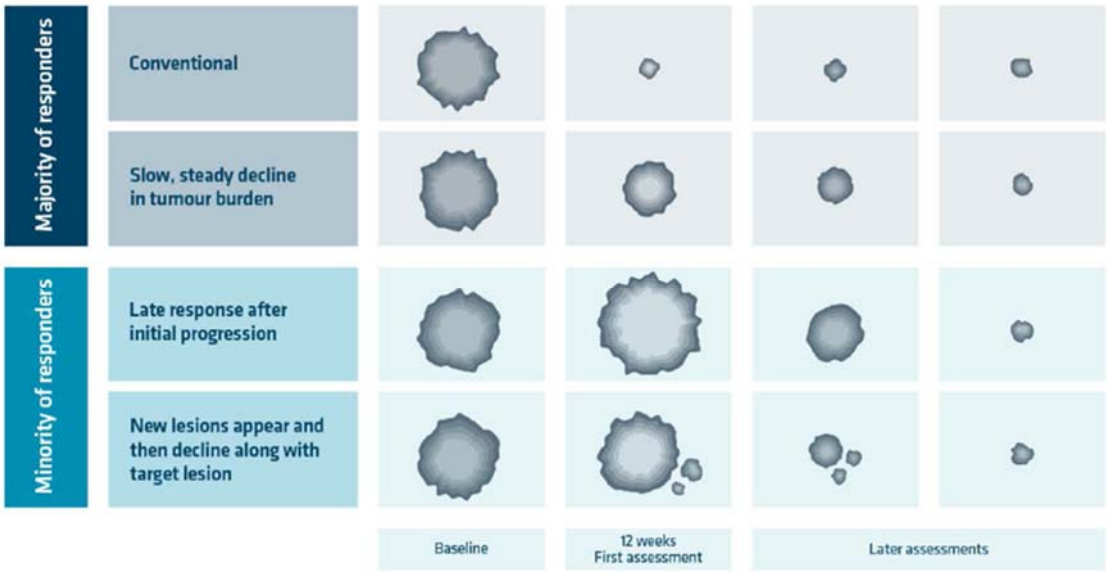


Key: OPDIVO, nivolumab; PD-1, programmed death-1; PD-L1, programmed-death ligand 1, PD-L2, programmed-death ligand 2.

There are key differences with these immunotherapy agents when compared to standard anti-cancer therapies, as a result of their novel mechanism of action. These differences are summarised below:

- Varying patterns of response can be observed with immunotherapy agents-oncology therapies such that patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment (Figure 3).
    - In some cases, increased T-cell activity and T cell infiltration of the tumour mass, may make the tumour appear bigger on a radiology scan (tumour flare) which falsely mimics progression (as defined by RECIST criteria);
    - This phenomenon of tumour flare (growth of existing lesions or the appearance of the new lesions) with immunotherapy, may precede antitumor effects[6];

Figure 3: Typical patterns of response observed with immunotherapy



- Immunotherapies are not regarded as targeted therapies. While they target specific pathways in the immune system, this is not the same as targeting a mutation on or within the tumour itself. In RCC, there are a number of reasons why PD-L1 expression should not be considered valid for informing clinical practice[7, 8];
    - PD-L1 tumour expression is an inducible marker with a transient/dynamic nature such that biopsy at baseline may not be reflective of PD-L1 tumour expression at response or progression;
    - There is no standard by which PD-L1 tumour expression is measured; various assays available use different antibodies, different staining protocols, different target cell assessment, different biopsies (fresh or archival), different scoring methods and different thresholds for defining a positive test result;
    - Other cell types that express PD-L1 may be present in the tumour microenvironment;
    - Tumours may express PD-L2, which also has immunological activity with the PD-1 receptor;

- Response to PD-1 inhibitor therapy is observed irrespective of PD-L1 tumour expression across a number of tumour types including renal cell carcinoma (RCC) (see Section 4.7)

This is consistent with the clinical trial data to be discussed in this submission as well as, advice received from UK clinicians at previous NICE appraisal committee meetings for PD-1 checkpoint inhibitor therapies for melanoma[9-11] and supported by UK RCC-treating oncologists and UK pathologists at recent advisory board meetings on RCC and biomarkers, respectively.[12, 13]

2.2 Marketing authorisation and health technology assessment

The indication for nivolumab of interest to this appraisal is as follows:

Opdivo® as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

This indication is based upon the results of CheckMate 025, a Phase III, randomised, open-label study of nivolumab versus everolimus in patients with advanced or metastatic clear-cell RCC (referred to herein as advanced RCC) who received prior anti-angiogenic therapy (see Section 4).

Marketing authorisation application for this indication was submitted to the European Medicines Agency (EMA) in October 2015 and a positive opinion from the Committee for Human Medicinal Products (CHMP) was received on 25 February 2016; European marketing authorisation is expected in April 2016. The summary of product characteristics (SmPC) is provided in Appendix 1 and the European public assessment report can be provided when available.

On 12th February, after a positive scientific opinion by the Medicines and Healthcare products Regulatory Agency (MHRA), BMS opened an Early Access to Medicines Scheme (EAMS) for adult patients with advanced renal cell carcinoma after prior therapy. The scheme will allow eligible patients to access nivolumab, funded by BMS, prior to the Marketing Authorisation. At the point of Marketing Authorisation in this indication, no new patients will be enrolled, although existing patients on the program will continue to receive nivolumab treatment. The scheme is open to

patients in England, Scotland, Wales and Northern Ireland. Since being open for 2 weeks, ten patients have been enrolled onto the EAMS program to receive nivolumab for advanced RCC after prior therapy.

Nivolumab (Opdivo®) as monotherapy already has marketing authorisation in the UK, Europe, and elsewhere for the treatment of advanced (unresectable or metastatic) melanoma in adults and for the treatment of locally advanced or metastatic squamous non-small cell lung cancer after previous chemotherapy in adults.

It is anticipated that Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) will submit nivolumab for advanced RCC for health technology assessment to the Scottish Medicines Consortium and the National Centre for Pharmacoeconomics in the Republic of Ireland following receipt of a positive CHMP opinion.

2.3 Administration and costs of the technology

Details of the administration of nivolumab are presented in Table 3.

Table 3: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate)	SmPC
Acquisition cost (excluding VAT) *	£439.00 for 40mg vial £1,097.00 for 100mg vial	List price
Method of administration	Intravenous infusion.	SmPC
Doses	3mg/kg	SmPC
Dosing frequency	Every 2 weeks.	SmPC
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Median duration of treatment in pivotal trial of 5.5 months.	SmPC CheckMate 025 trial data
Average cost of a course of treatment	£66,426 treatment cost excluding administration costs, £71,260 treatment cost including administration costs.	Economic model. Also reported: Tables 69-71, Section 5.7.3
Anticipated average interval between courses of treatments	Retreatment is not anticipated	-
Anticipated number of repeat courses of treatments	Retreatment is not anticipated	-
Dose adjustments	Dose escalation or reduction is not recommended	SmPC
Anticipated care setting	Hospital or clinic setting	SmPC

Key: SmPC, Summary of Product Characteristics
Notes: * Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.4 Changes in service provision and management

Nivolumab is not a targeted therapy, and as such, additional tests or investigations outside of those required for the diagnosis of advanced RCC are not needed.

Nivolumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of nivolumab would utilise this existing National Health Service (NHS) infrastructure, although there may be a need for additional infrastructure/resource to accommodate regular intravenous (IV) administration in some units given current treatment options are oral in nature (see Section 3.2). Conversely, IV administrations will likely increase adherence to therapy (as recently demonstrated in metastatic RCC[14]), which may save NHS resources attributed to possible consequences of non-compliance with oral medications in the longer-term.

Patients treated with nivolumab should also be regularly monitored for signs or symptoms of Select adverse events (AEs) with a potential immunological cause, as early identification of AEs and intervention are an important part of the safe use of nivolumab. Clinicians practicing across indications will be familiar with monitoring patients for Select AEs as this is recommended for all patients receiving immunotherapy. Detailed safety algorithms are available for clinicians less familiar with immunotherapy drugs (Appendix 1). No concomitant therapies are specified in the marketing authorisation for nivolumab, but treatments for AE management are recommended as required (Appendix 1).

Staff and administration costs as well as costs for monitoring, tests and AE management are all fully accounted for in the economic modelling presented in Section 5.

2.5 Innovation

Significant advancements in RCC therapeutics were made with the introduction of targeted therapy, but no other distinctly novel products have entered the market since their initial introduction; as a result, sequencing of the same treatment class is often observed in the current clinical pathway of care (see Section 3.2). Nivolumab is the first checkpoint inhibitor immunotherapy to file for marketing authorisation in advanced RCC providing an innovative mechanism of action that utilises the body's own immune system to destroy cancer cells (see Section 2.1). Following a positive

scientific opinion by the MHRA, nivolumab is the first immunotherapy available for patients with advanced RCC after prior therapy through an EAMS.

Active treatment options for patients with advanced RCC who have received prior therapy have no proven overall survival (OS) advantage, and assumptions of longer-term benefit are based on the primary endpoint analysis of progression-free survival (PFS) in registrational trials. Furthermore, active treatment options can be associated with toxicity profiles that may counteract positive benefit from clinical efficacy on patient quality of life (see Section 3.5). Nivolumab is the first therapy to demonstrate a significant OS benefit in patients with advanced RCC who have received prior therapy in a Phase III trial setting. In the pivotal regulatory trial, CheckMate 025, nivolumab significantly improved median OS by over 5 months compared with the targeted therapy, everolimus (see Section 4.7). Furthermore, nivolumab resulted in constant improvement in disease-specific patient quality of life (assessed with the use of the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms [FKSI-DRS] scoring algorithm) and demonstrated a favourable safety profile compared with a targeted therapy option.

While we would anticipate health-related benefits will be captured in the quality-adjusted life year (QALY) calculation, their significance to patients along with the fact that nivolumab provides the first checkpoint inhibitor immunotherapy option for advanced RCC in over a decade for patients who have received prior therapy, should be viewed as innovative. Indeed, the introduction of nivolumab would change the treatment paradigm for such patients and thus represents a ‘step-change’ in the management of this condition, offering an interruption to same class sequencing utilised in current clinical practice and potentially improving the life-expectancy of patients with advanced RCC.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Kidney cancer is the seventh most common cancer in the UK (based on the most recent data available [2013]), but is still relatively rare, accounting for only 3% of all new cancer cases.[15] There are two main types of kidney cancer observed in adults, transitional cell cancer of the renal pelvis and RCC, where cancerous cells develop within the epithelia of the renal tubules; RCC is the most common type, responsible for approximately 80% of all cases of kidney cancer diagnosed in the UK.[15, 16]Histologically, RCC is usually observed as clear cells, and clear-cell RCC comprise approximately 75% of all cases of RCC.[15, 17-19]

Importantly for this submission (and like melanoma for which nivolumab has recently been recommended for use by NICE[11]) RCC is seen as an immunogenic tumour (and thus conducive to immunotherapy treatments) based on the following:

- The high level of tumour T-cell infiltration seen[17, 18, 20];
- The observed instances of spontaneous regression of metastatic lesions, following immune stimulation triggered by debulking kidney surgery[21, 22];
- Advanced RCC's response to IL-2 cytokine immunotherapy, historically, that has shown to result in durable long-term responses in a proportion of patients (~10%).[16, 17, 20, 23]

Aetiology, course and prognosis

Many environmental and clinical factors are implicated in the aetiology of RCC. The most common risk factors for developing RCC include smoking and obesity, with an estimated 42% of kidney cancers in the UK attributed to these factors.[15] Additional risk factors include hypertension, diabetes, renal failure, occupational exposure to toxic compounds such as asbestos, analgesic drug abuse, genetic conditions such as familial history of kidney cancer and Von Hippel Lindau (VHL) mutations.[15, 22, 24-28]

Demographically, more than a third (35%) of cases of kidney cancer in the UK are diagnosed in people aged 75 or over with diagnosis in people under 50 being rare.[15] In addition, men are up to two times more likely to develop RCC than women; in the UK, kidney cancer accounts for 4% of all new cancer cases in males compared with 3% of all new cancer cases in females.[15, 29, 30]

As with other forms of cancer, RCC is divided into stages that describe how widespread the disease has become; the most common staging system utilised is the American Joint Cancer Committee (AJCC) Tumour Node Metastasis (TNM) staging system which classifies the size of the tumour (T), the involvement of regional lymph nodes (N) and the presence of distant metastases (M). Localised RCC (Stage I) is confined to the kidney and is potentially curable with surgical resection; indeed, approximately 90% of patients with Stage I RCC will survive for 5-years or more post diagnosis.[31] However, advanced RCC has a poorer outlook with no cure (5 year survival rate approximately 10-15%[31]; see Section 3.3). Approximately 27% of RCC is diagnosed at stage IV, where there is tumour invasion through the fascia ligament covering the kidney; direct tumour extension to the adjacent adrenal gland or spread to distant organ(s), such as the lung, liver, bone and brain.[15, 31] In addition to patients presenting with advanced disease, some treated for earlier stage RCC may subsequently relapse and develop advanced disease.

There are two main scoring systems used to specifically assess prognosis in individual patients with advanced RCC: the Memorial Sloane Kettering Cancer Centre (MSKCC) score and a slightly modified version, known as the International Metastatic RCC Database Consortium (IMDC) or Heng criteria.[26] In the MSKCC scoring system, the presence of five criteria (Karnofsky performance status <80%; haemoglobin < the lower limit of normal [LLN]; time from diagnosis to systemic treatment of <1 year; corrected calcium >upper limit of normal [ULN] lactate dehydrogenase > 1.5 times ULN) are added up (one point for each criteria) to categorise the patient into favourable (no points), intermediate (1-2 points) and poor risk (3-5 points) groups, which are associated with worsening predicted survival. [26] Both scoring systems have been validated for use in the era of targeted therapies for advanced RCC.[27] Of specific interest in consideration of the nivolumab mechanism

of action (see Section 2.1), some studies have also suggested that PD-L1 expression in RCC is associated with a poor prognosis, presumably because of its immunosuppressive function.[32-34]

Burden of disease

In the early stages of disease, RCC is relatively asymptomatic and often detected incidentally during medical investigation for other conditions.[26] When symptoms do occur, often as a result of disease progression, those classically observed include gross haematuria (blood in the urine), pain or discomfort in the upper abdomen or back (flank pain) and a palpable lump or mass in the kidney area; patients with metastatic disease may also present with symptoms due to metastases.[15, 26]

The symptoms of advanced disease and the generally poor prognosis for patients with advanced RCC can also significantly impact individual patients' everyday lives and overall wellbeing.[29, 35-37] Advanced RCC impacts on all domains of patient health-related quality of life (HRQL) including physical and psychosocial function.[29] It is important to note that patient HRQL can also be further reduced as a result of significant toxicities related to treatment for advanced RCC (see Section 3.5).

In addition to patient burden, advanced RCC can also present significant burden to informal caregivers and wider society, primarily as a result of direct care requirements and reduced life expectancy; both of which are worsened with disease progression.[29, 38-40] In consideration of the ageing population and the rising prevalence of risk factors such as obesity, particularly in industrialised countries, the incidence of advanced RCC is increasing worldwide. The burden of advanced RCC is therefore predicted to increase significantly[29, 41], highlighting the need for further advancements in the treatment of this disease.

3.2 Clinical pathway of care

As potentially curative surgery is not a treatment option for patients with advanced RCC, international clinical guidelines are aligned in their recommendation that such patients should foremost be considered for treatment with systemic therapy based on targeted agents.[26, 27] This is due to the fact that targeted agents have

demonstrated significant clinical benefit over traditional chemotherapy and cytokine based immunotherapy treatments.

While the clinical pathway of care in England does reflect these guidelines, NICE currently only recommends the use of one class of targeted agent: vascular endothelial growth factor receptor [VEGFR] tyrosine kinase inhibitors (TKIs), which target angiogenic signalling. The only other active treatment option available for patients with advanced RCC who have received prior therapy in England is everolimus, a mammalian target of rapamycin (mTOR) inhibitor that targets the PI3K pathway responsible for cell survival signalling. While NICE does not recommend everolimus, this agent is currently available through the Cancer Drugs Fund (CDF) under specific circumstances.

Systemic therapies considered to be established standard of care for the treatment of advanced RCC in NHS England are detailed in Table 4.

Table 4: Established standard of care systemic therapies for the treatment of advanced RCC in NHS England

Product (brand)	Treatment class	Posology and administration	Marketing authorisation	NICE recommendation	Current use estimates
Pazopanib (Votrient®)	VEGFR TKI	800mg oral tablet once daily.	Indicated in adults for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease.	Recommended as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an ECOG PS of 0 or 1.	[redacted] market share in the first-line setting. [redacted] market share in the subsequent-line (second/third) setting.
Sunitinib (Sutent®)	VEGFR TKI	50mg oral tablet once daily for 4 weeks followed by a 2 week rest period; repeated 6 week cycle.	Indicated for the treatment of advanced/metastatic RCC in adults.	Recommended as a first-line treatment option for people with advanced RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1. Not recommended as a second-line treatment option.	[redacted] market share in the first-line setting. [redacted] market share in the subsequent-line (second/third) setting.
Axitinib (Inlyta®)	VEGFR TKI	5mg oral tablet twice daily.	Indicated for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.	Recommended for the treatment of adult patients with advanced RCC after failure of prior treatment with a first-line TKI or a cytokine; statutory funding only available for treatment as per licence terms.	[redacted] market share in the second-line setting. [redacted] market share in the third-line setting.
Everolimus (Afinitor®)	mTOR inhibitor	10mg oral tablet once daily.	Indicated for the treatment of patients with advanced RCC, whose disease has progressed on or after	Not recommended by NICE, but available through the CDF for patients with metastatic RCC who have had prior treatment with only one previous TKI and are contraindicated to second-line	[redacted] market share in the second-line setting.

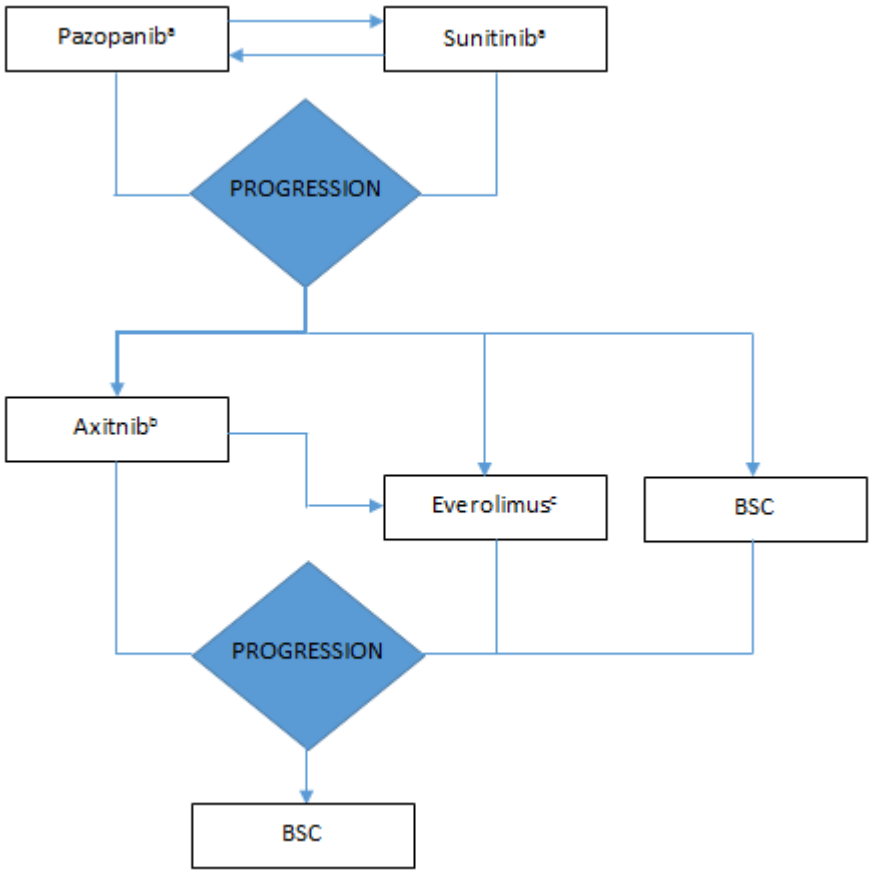
Product (brand)	Treatment class	Posology and administration	Marketing authorisation	NICE recommendation	Current use estimates
			treatment with VEGF-targeted therapy.	axitinib therapy or show excessive toxicity to axitinib within the first 3 months of treatment initiation and have no evidence of disease progression.	[redacted] market share in the third-line setting.[a]

Key: CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PS, performance status; RCC, renal cell carcinoma; SmPC, of Product Characteristics; TKI, tyrosine-kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Notes: [a], this can be expected to decrease with everolimus use in the third-line setting being delisted from the CDF in November 2015.
Source: Axitinib SmPC[42]; Everolimus SmPC[43]; NICE guidance for renal cancer[44]; Market landscape overview[45]; Pazopanib SmPC[46]; Sunitinib SmPC.[47]

Patients who fail first-line treatment, but for whom further systemic therapy with targeted agents is not suitable (for example, patients who are considered too unwell to tolerate such treatments), have no active treatment option in current clinical practice and management options are restricted to best supportive care (BSC) or clinical trial enrolment (if an appropriate trial is available). BSC is also the only management option for patients who fail axitinib in the second-line setting with everolimus in the third-line setting delisted from the CDF in November 2015.[48]

The current clinical pathway of care for advanced RCC in NHS England is presented in Figure 4. This pathway portrays patients moving from first- to second-line treatment on confirmation of disease progression; while reflective of clinical practice, it should be noted that due to restrictions and limitations with current treatment options in the second-line setting (see Section 3.5), oncologists report persevering with first-line treatment post suspected disease progression in current practice (providing patients can tolerate continuing therapy).[12]

Figure 4: Current clinical pathway of care for advanced RCC in NHS England



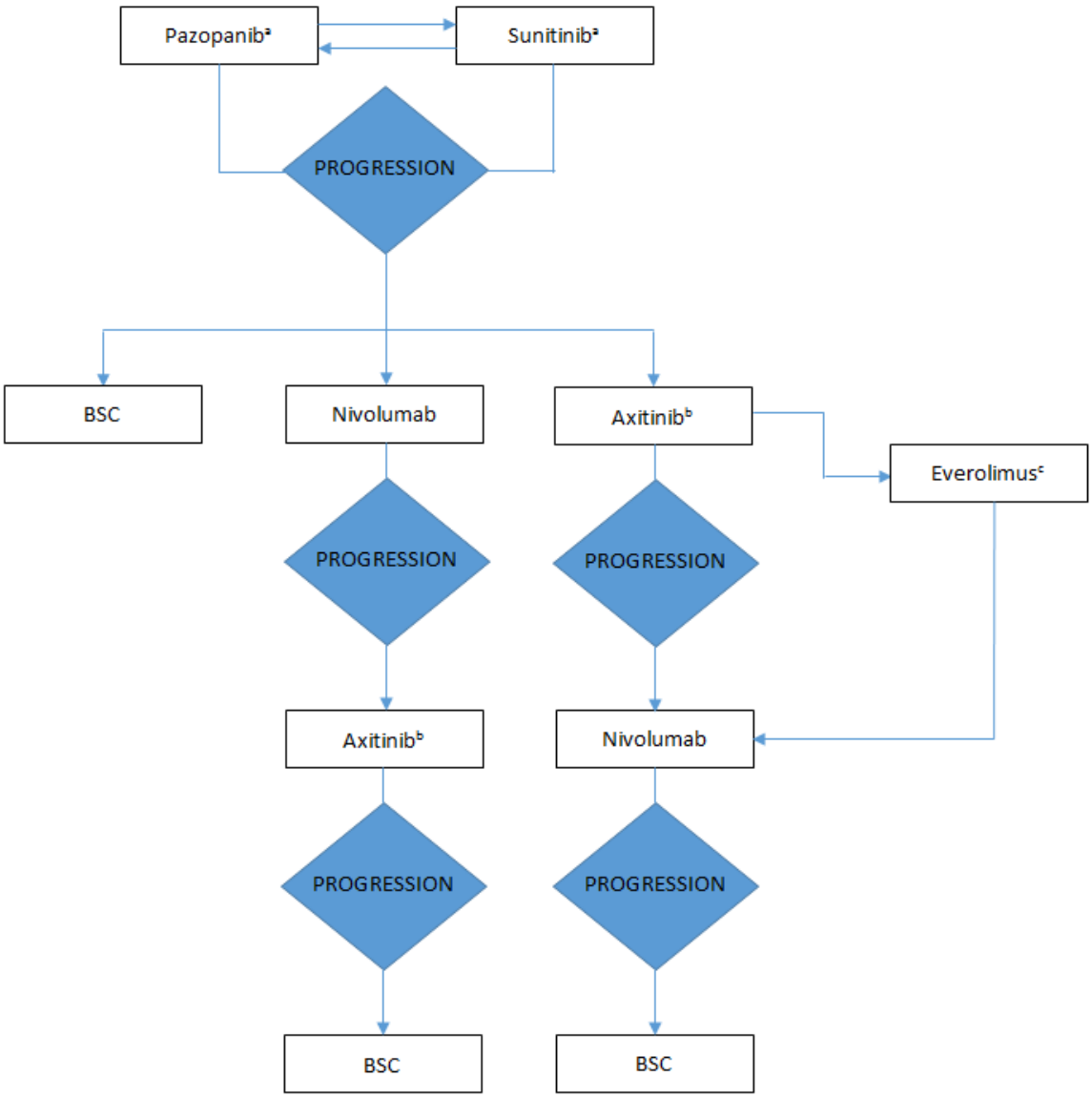
Key: BSC, best supportive care; NHS, National Health Service; RCC, renal cell carcinoma.
Notes: [a], patients who have not progressed and do not tolerate first-line pazopanib can switch to sunitinib and vice versa; [b], routinely funded only for patients who receive sunitinib at first-line; [c], patients may receive everolimus only if they are contraindicated to axitinib or have excessive toxicity to axitinib and discontinue treatment within 3 months.

Nivolumab provides a novel treatment option with proven OS and HRQL benefit for patients with advanced RCC who have received prior therapy (see Section 4.7). Nivolumab offers an interruption to the current standard of VEGFR TKI- VEGFR TKI sequencing, reducing the risk of resistance and excessive overlap of similar side-effects between first- and second-line treatments (see Section 3.5). In consideration of its favourable safety profile, nivolumab may also offer an active treatment option to a small proportion of patients who are considered too unwell to tolerate further targeted therapy at second-line (currently managed with BSC). In addition,

nivolumab offers an active treatment option for patients who have exhausted all treatment options available in current practice.

The future clinical pathway of care for advanced RCC if nivolumab is recommended for use in accordance with its licence terms is depicted in Figure 5.

Figure 5: Future clinical pathway of care for advanced RCC in NHS England if nivolumab is recommended for use



Key: BSC, best supportive care; NHS, National Health Service; RCC, renal cell carcinoma.
Notes: [a], patients who have not progressed and do not tolerate first-line pazopanib can switch to sunitinib and vice versa; [b], routinely funded only for patients who receive sunitinib at first-line; [c],

patients may receive everolimus only if they are contraindicated to axitinib or have excessive toxicity to axitinib and discontinue treatment within 3 months.

While nivolumab therefore provides a treatment option for all subsequent-line settings, a panel of RCC-treating oncologists in the UK unanimously stated they would preferentially use nivolumab in the second-line setting during recent clinical consultation.[12] Furthermore, availability of an effective second-line treatment option was predicted to reduce the rate of first-line treatment perseverance despite suspected disease progression and may result in patients being given earlier access to systemic therapy. [12] This potential of nivolumab to change treatment paradigms for patients with advanced RCC has recently been acknowledged by the European Association of Urology who released an update to their guidelines, recommending nivolumab as a second-line treatment option with an OS advantage.[49] Nivolumab was also added as an option to treat advanced RCC after VEGFR TKI therapy in the recent update to the National Comprehensive Cancer Network (NCCN) guidelines in the US.[28]

3.3 Life expectancy, prevalence and incidence of the disease

Life expectancy

Long-term survival is rarely observed in patients diagnosed with advanced RCC with 5-year survival rates of 10-15% associated with Stage IV disease in the UK.[31] For patients with advanced disease who have received prior therapy, median OS estimates associated with active subsequent-line treatments available in current practice is less than 20 months with few patients estimated to survive past 3 years (based on clinical trial data).[50, 51] For patients who cannot tolerate further treatment, life-expectancy is understandably worse with median OS estimates of less than 12 months associated with BSC post first-line therapy failure in real-world studies.[52, 53]

Population estimates

In 2013, the incidence of kidney cancer in England was 8,505.[54] Through 2005 to 2013, the average annual increase in kidney cancer incidence was approximately 6%[55]. Applying the same annual incidence rate for the following 3 years, the predicted incidence of kidney cancer in England for 2016 is 10,130. Assuming that

80% of all cases of kidney cancer are RCC[15, 16] and that 30% of all cases of RCC are advanced at diagnosis[18, 56-59], the predicted incidence of advanced RCC in England for 2016 is 2,431.

Of all patients diagnosed with advanced RCC in the UK, up to 75% are estimated to receive systemic therapy at first-line[45, 60], of which most will progress. Applying this to the above figures, there will be an estimated 1,823 patients with advanced RCC who have received at least one line of prior therapy in England. It should be acknowledged that this estimate should be treated with caution as it does not incorporate prevalence data or accommodate for death within the first year of diagnosis (despite active treatment). This is due to the fact that prevalence data and up to date 1-year survival estimates reflecting current practice are not readily available and therefore cannot be applied.

Severity of disease or concerns over general health (patients not considered fit enough to tolerate further targeted therapy [see Section 3.2; 3.5]) can also result in patients not receiving subsequent therapy. In current clinical practice, UK experts suggest that approximately half of patients receiving first-line systemic therapy actually go on to receive second-line treatment.[12, 60]

3.4 Clinical guidance and guidelines

NICE guidance

There are a number of NICE guideline and guidance documents and published technology appraisal guidance relating to renal cancer:

- NICE Guidance on Cancer Services
  - September 2002. ‘Improving outcomes in urological cancers’. CSG2.
- NICE Technology Appraisal Guidance
  - February 2015. ‘Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment’. TA333.[61]
  - April 2011. ‘Everolimus for the second-line treatment of advanced renal cell carcinoma’. TA219.[62]

- February 2011. ‘Pazopanib for the first-line treatment of advanced renal cell carcinoma’. TA215.[63]
- August 2009. ‘Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma’. TA178.[64]
- March 2009. ‘Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma’. TA169.[65]

Clinical guidelines

There are also a number of clinical guidelines relating to RCC that are relevant to current clinical practice in England:

- European Association of Urology: Guidelines on renal cell carcinoma (2015).[27]
  - Updated European Association of Urology Guidelines for clear cell renal cancer patients who fail VEGF targeted therapy (2016).[49]
- Renal cell carcinoma: European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014).[26]
- The National Comprehensive Cancer Network clinical practice guidelines in oncology, kidney cancer (v2.2016.[28]

3.5 Issues relating to current practice

In the absence of a cure for advanced RCC, goals of treatment are to extend life and delay disease progression while relieving physical symptoms and maintaining physical function.[64] Due to restricted treatment choice and limitations with treatments that are available, these goals are not being met for many patients with advanced RCC who have received prior therapy.

Key issues with current treatment options are summarised in Table 5.

Table 5: Key issues with current treatment options for patients with advanced RCC who have received prior therapy

Treatment	Summary of key issues
Axitinib	• No proven OS benefit for patients with advanced RCC who have received prior therapy – No Phase III trial designed to assess OS in this population – No OS benefit compared with alternative VEGFR TKI treatment (sorafenib) in the second-line setting: HR for death: 0.97 (95% CI, 0.08, 1.17); p=0.37[50] – Limited OS benefit compared with mTOR inhibitor therapy for patients who have received prior therapy (see Section 4.10) • No positive impact on HRQL when used to treat patients with advanced RCC in the second-line setting – No noticeable change in FKSI-15, FKSI-DRS or EQ-5D scores during treatment[66] – No significant difference between HRQL compared with alternative TKI treatment[66] • Limitations of same class of treatment as those used to treat patients with advanced RCC in the first-line setting – Potential for RCC tumours to develop acquired or adaptive resistance to targeted therapy[67] – Antiangiogenic therapy acquired resistance after first-line treatment is supported by the reduced survival benefit seen in patients treated with prior VEGFR TKI therapy compared with prior cytokine therapy in the second-line setting[50], – Risk of excessive overlap of similar side-effects (particularly concerning to patients who suffer treatment-related toxicity with first-line VEGFR TKI treatment) • Concerns over tolerability with high rates of dose reductions and AEs reported in the regulatory trial – 34% (121/359) of patients required dose reductions in the second-line setting[50] – High rates (≥10%) of Grade 3 or more hypertension, diarrhoea and fatigue[50] – 11% of patients experienced haemorrhage; 4 reported treatment-related or causality-unknown deaths[68, 69]
Everolimus	• No proven OS benefit for patients with advanced RCC who have received prior therapy – No Phase III trial designed to assess OS in this population (prior to CheckMate 025, see Section 4) – No OS benefit compared with BSC in the subsequent-line setting (though analyses confounded by high rates of crossover)[70]

Treatment	Summary of key issues
	– Limited OS benefit compared with VEGFR TKI therapy for patients who have received prior therapy in modelled estimates (see Section 4.10) • No positive impact on HRQL when used to treat patients with advanced RCC in the subsequent-line setting – No significant difference in time to definitive deterioration of the FKSI DRS score compared with placebo[70] • Concerns over tolerability with high rates of dose interruptions and AEs reported in regulatory trial – 35% of patients (96/274) required dose interruptions due to AEs in the subsequent-line setting[70] – High rates (≥10%) of Grade 3 or more infections[70] – 4 reported infection-related or respiratory failure deaths [70] • Not recommended by NICE for routine funding in NHS England – Only available to a small group of patients as per CDF criteria
BSC	• No long-term clinical benefit for patients with advanced RCC who have received prior therapy – Used to manage symptoms in an attempt to minimise impairment of HRQL during final stages of disease – Associated with median life-expectancy of <12 months[52, 53]
Key: AE, adverse event; BSC, best supportive care; CI, confidence interval; EQ-5D, EuroQol-five dimension; FKSI-15, 15 item Functional Assessment of Cancer Therapy Kidney Symptom Index; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; HR, hazard ratio; HRQL, health-related quality of life; mTOR, mammalian target of rapamycin; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.	

There is a clear unmet medical need for a tolerable treatment option with a proven OS benefit, a favourable safety profile and quality of life benefit for patients with advanced RCC who have received prior therapy. Nivolumab meets this unmet need.

3.6 Assessment of equality issues

No equality issues related to the use of nivolumab have been identified or are foreseen.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

Search strategy

A systematic literature review designed to identify randomised controlled trials (RCTs) of nivolumab and comparator therapies used in the second- and subsequent-line treatment of advanced RCC was initiated in November 2014.

Information retrieval methods were based upon the research question "What is the relative efficacy and safety of nivolumab as compared to other licensed and investigational agents used for the second or later line treatment of RCC?"

Searches were performed in global electronic databases:

- Embase
- MEDLINE and MEDLINE-In-Process
- Cochrane Central Register of Controlled Trials

In addition, annual proceedings of the following conferences were hand-searched for the last three years (from 2012-2015):

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU) Symposium
- European Society for Medical Oncology (ESMO)

The full search strategies used are presented in Appendix 2.

Reference lists of relevant systematic reviews and meta-analyses were also hand-searched to highlight any further relevant studies and unpublished data held by BMS were reviewed for relevance to the research question/decision problem.

Study selection

The full eligibility criteria applied to the identified evidence base is presented in Table 6. Of note, this review was conducted from a global perspective, and therefore a

number of comparators were included which are not relevant to a UK setting (and not named in the decision problem).

All controlled clinical trials (RCTs irrespective of blinding status) were included in the final evidence base of relevant studies if they investigated the clinical efficacy and/or safety of nivolumab or comparator agents. Outcomes of interest were those considered representative of the clinical benefit and safety measures adopted in clinical practice and those named in the decision problem. However, trials were not excluded on the basis of outcome alone. RCTs were included regardless of design (parallel, cross-over, and open-label, single- or double-blinded).

Table 6: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced RCC Previously treated patients	Patients with localised RCC Paediatric RCC patients Patients with non-RCC disease Treatment naïve patients
Intervention	Bevacizumab + α-interferon α-interferon Interleukin-2 Everolimus Temsirolimus Sorafenib Sunitinib Pazopanib Axitinib Cediranib Cabozantinib Nivolumab Nafatumomab IMA901 BNC105P Dalantercept TRC105P GDC-0980	Any other
Comparator	Any treatment from the above included list of interventions	None

	Placebo Best supportive care	
Outcomes	Overall survival Progression free survival Response rate Duration of response Time to progression Quality of life Safety and tolerability	None
Study design	Randomised controlled trials Systematic reviews/meta-analyses[a]	Non-randomised controlled trials Single-arm trials Observational studies Database analyses Pooled data analyses Non-systematic reviews In-vitro studies Preclinical studies Case reports/series Commentaries/letters/editorials
Language restrictions	English language only	None
Key: RCC, renal cell carcinoma. **Notes**: [a], included for reference review only		

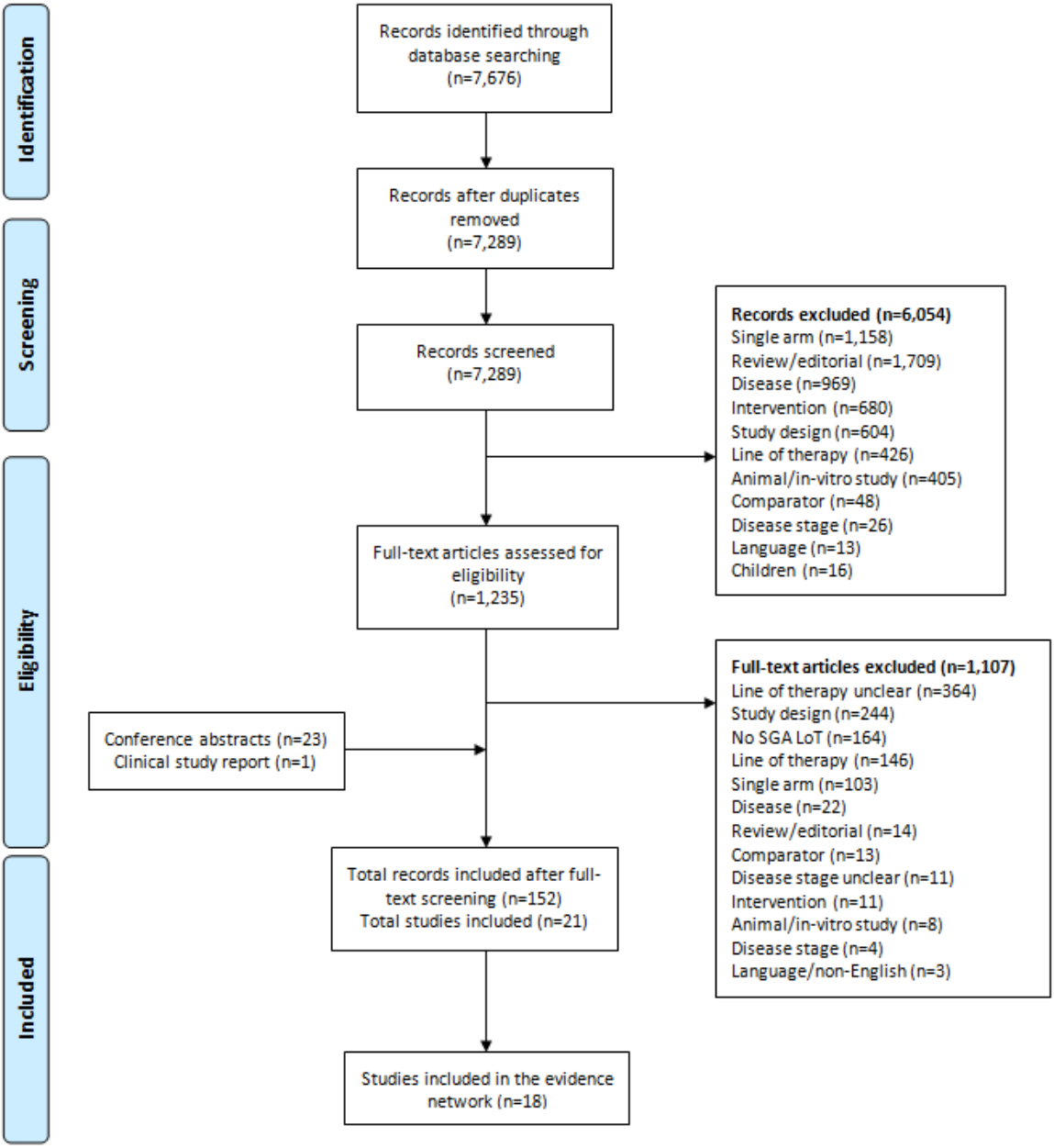
Two reviewers independently inspected each reference (title and abstract) identified by the literature searches and applied basic study selection criteria based on the eligibility criteria presented in Table 6 (primary screening). Citations meeting basic study selection criteria (or in cases of disagreement between the two reviewers) were obtained in full and independently assessed against full eligibility criteria presented in Table 6 (secondary screening). In the event of disagreement between the two reviewers, a third reviewer independently assessed the paper and applicability of selection criteria attained by consensus.

If study duplication within publications was suspected, author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted, but this situation did not occur. Where multiple publications were identified for the same clinical trial, all were included in the final list of articles

meeting the eligibility criteria, but clearly identified as primary and secondary sources of data for the same trial.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the systematic review is shown Figure 6.

Figure 6: PRISMA flow diagram of the literature search process



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SGA LoT, subgroup analysis for line of therapy.

A total of 7,676 records were identified through database searches and after removal of duplicates (n=387), primary screening was carried out on 7,289 records. Of these, 6,054 were excluded as they were not of relevance to the research questions. Common reasons for exclusion at primary screening included non-RCT study design, non-advanced RCC patients and investigations of interventions not of relevance to the research question.

Of the 1,235 records accessed in full for further evaluation, 128 reported results for studies meeting the eligibility criteria of the review (Table 6). Conference proceeding searches identified an additional 23 abstracts and one clinical study report (CSR) of unpublished data that were also included in the final evidence base. Therefore, after full text screening a total of 152 records were included; these records reported on 21 unique studies, 18 of which could be connected within an evidence network for potential meta-analyses (see Section 4.10). Primary data sources for studies included in the final database are listed in Table 7; secondary data sources are presented in Appendix 3.

Table 7: Primary data sources for RCTs included in the final evidence base

Trial name	Treatment arms	Primary data source
AXIS	Axitinib vs sorafenib	Rini et al. 2011[68]
CheckMate 025	Nivolumab vs everolimus	CheckMate 025 CSR[a71]
CRECY	Interleukin-2 vs interleukin-alfa-2a	Escudier et al. 1999[72]
DISRUPTOR-1	Everolimus plus BNC105P vs everolimus	Pal et al. 2015[73]
ESPN	Everolimus vs sunitinib	Tannir et al. 2014[74]
GOLD	Dovitinib vs sorafenib	Motzer et al. 2014[75]
Guo et al. 2015	Bevacizumab vs sorafenib	Guo et al. 2015[76]
INTORSECT	Temsirolimus vs sorafenib	Hutson et al. 2014[77]
Motzer et al. 2015	Lenvatinib plus everolimus vs lenvatinib vs everolimus	Motzer et al. 2015[78]
Patel et al. 2008	Interleukin-2 plus SRL172 vs interleukin-2	Patel et al. 2008[79]
Powles et al. 2014	Apitolisib vs everolimus	Powles et al. 2014[80]
Qin et al. 2012	Axitinib vs sorafenib	Qin et al. 2012[81]
Ratain et al. 2006	Sorafenib vs placebo	Ratain et al. 2006[82]
RECORD-1	Everolimus plus BSC vs placebo plus BSC	Motzer et al. 2008[51]
RECORD-3	Everolimus vs sunitinib	Motzer et al. 2014[83]
SWITCH	Sunitinib vs sorafenib	Eichelberg et al. 2014[84]
TARGET	Sorafenib vs placebo	Escudier et al. 2007[85]
TIVO-1	Tivozanib vs sorafenib	Motzer et al. 2013[86]
VEG105192	Pazopanib vs placebo	Sternberg et al. 2010[87]
Walter et al. 2012	IMA901 plus GM-CSF plus cyclophosphamide vs IMA901 plus GM-CSF	Walter et al. 2012[88]
Yang et al. 2003	Bevacizumab 10mg vs bevacizumab 3mg vs placebo	Yang et al. 2003[89]

Key: BSC, best supportive care; CSR, clinical study report.
Notes: [a], published since the time of review (see Section 4.2).

Data extraction for each study meeting the eligibility criteria (Table 6) was undertaken by two independent reviewers with any discrepancies between reviewers reconciled by a third independent reviewer.

Systematic searches for this review are currently being updated in acknowledgement of the fact that they were initiated over 12 months ago. In the absence of a standard STA timescale, it has not been possible to complete this update in time for this submission but full details can be provided at clarification questions.

Evidence identified and providing data for nivolumab are presented in Sections 4.2 to 4.8 and Section 4.12. Sources which present data for comparator agents are only utilised in network meta-analyses (NMA) and presented in Section 4.10.

4.2 List of relevant randomised controlled trials

The Phase III RCT, CheckMate 025, provides evidence on the clinical benefit of nivolumab 3mg/kg within the indication being appraised, as detailed in Table 8.

This trial was included in the systematic review evidence base in CSR form only[71], but has since been published in the New England Journal of Medicine.[90] Subgroup analyses have also recently been presented at the ASCO Genitourinary Cancers Symposium 2016.[91]

Table 8: List of relevant RCTs

Trial name (NCT number)	Population	Intervention	Comparator	Primary study reference
CheckMate 025 (NCT01668784)	Adult patients with advanced RCC with a clear-cell component who had received one or two previous regimens of antiangiogenic therapy	Nivolumab 3mg/kg IV every two weeks	Everolimus 10mg orally every day	Motzer et al. 2015[90]
Key: IV, intravenous; RCC, renal cell carcinoma; RCT, randomised controlled trial.				

CheckMate 025 directly compared the clinical efficacy and tolerability of nivolumab with everolimus; this was the most appropriate comparator at the time of study initiation as it was the only active treatment licensed for the treatment of advanced RCC patients who had received prior therapy. No head-to-head data are available

comparing nivolumab to axitinib or BSC in this population; their comparative efficacy has therefore been estimated using indirect comparison methods (see Section 4.10).

4.3 Summary of methodology of the relevant randomised controlled trials

A summary of the methodology of CheckMate 025 is summarised below and presented in Table 9.

CheckMate 025 is a phase III, multicentre, open-label RCT evaluating the safety and efficacy of nivolumab in comparison with everolimus in patients with advanced RCC previously treated with antiangiogenic agents.[71, 90]

The study was initiated in October in 2012 and data presented in this submission are based on a clinical database lock of 18th June 2015. This was originally planned as an interim database lock; however, the data monitoring committee (DMC) confirmed that the pre-specified boundary for OS benefit was crossed and noted there were no new safety signals, thus the study was terminated early to allow patients randomised to the control arm to receive nivolumab (see Section 4.4). The last subject was randomised on 11 March 2014, and the last patient's last visit date for this data cut occurred on 06 May 2015, providing a minimum follow-up of 14 months for all patients.

The primary endpoint in CheckMate 025 was OS, defined as the time from randomisation to the date of death. Secondary endpoints included objective response rate (ORR), PFS, the association between OS benefit and tumour expression of PD-L1, and the incidence of adverse events. These endpoints were considered clinically relevant measures of disease as used in clinical practice and are also consistent with previous studies exploring the use of other anti-cancer agents in this population. As part of the safety and tolerability review, particular attention was paid to the identification and assessment of AEs of specific interest which were immune-related and potentially associated with the use of nivolumab.

Of note, patients in the nivolumab arm could continue treatment beyond initial Response Evaluation Criteria in Solid Tumours (RECIST)-defined progression (where progression is based on tumour size and/or the appearance of new lesions) if

they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. This design is based on accumulating clinical evidence indicating that some patients treated with immune system-stimulating agents show disease progression, as defined by conventional RECIST criteria, before demonstrating subsequent clinical objective responses and/or stable disease.[92] The label for everolimus allows for continued treatment as long as clinical benefit is observed or until unacceptable toxicity occurs. Therefore, patients on the everolimus arm were also permitted to continue treatment beyond initial investigator-assessed RECIST-defined progression if they met the same criteria.

Outside of clinical trials, most radiologists do not report radiology scans using RECIST criteria[12] and in clinical practice, response to therapy will largely be based on clinical judgement, with consideration given to the potential of response, despite an initial increase in tumour burden or the presence of new lesions when treating with an immunotherapy agent (Figure 3). It is important to note that tumour progression assessments of immunotherapy drugs, using RECIST criteria for the definition of disease progression within clinical trials, provide a conservative estimate of benefit from therapy, as compared to the clinical assessment of benefit with immunotherapy.

Table 9: Comparative summary of trial methodology

	CheckMate 025
Location	Patients were treated at 146 sites in 24 countries including Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Norway, Poland, Romania, Russian Federation, Spain, Sweden, United Kingdom and United States
Trial design	A Phase III, randomised, open-label, active control, multi-centre clinical trial Patients were randomised 1:1 through an IVRS. Randomisation was stratified by MSKCC risk group, and number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting
Eligibility criteria for participants	Men and women aged ≥18 years who signed informed consent and met the following criteria were enrolled: • Histologically confirmed advanced or metastatic RCC with a clear-cell component; • Measurable disease according to RECIST v1.1;

	CheckMate 025
	• Received one or two previous regimens of antiangiogenic therapy; • No more than three total previous regimens of systemic therapy; • Disease progression during or after the last treatment regimen and within 6 months before study enrolment; • Karnofsky PS ≥70 Patients who met any of the following key criteria were excluded from study eligibility: • Metastasis to the CNS; • Previous treatment with an mTOR inhibitor; • Condition requiring treatment with glucocorticoids (equivalent to >10mg prednisone daily)
Settings and locations where the data were collected	Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. The DMC acted in an advisory capacity to BMS, monitoring subject safety and evaluating the available efficacy data for the study.
Trial drugs	Nivolumab group (n=410): nivolumab 3mg/kg by IV infusion every 2 weeks Everolimus group (n=411): everolimus administered orally at a daily dose of 10mg Patients were treated until progression or unacceptable toxicity. Patients were allowed to continue the study therapy after initial disease progression if a clinical benefit as assessed by the investigator was noted and the study drug had an acceptable side-effect profile. Dose modifications were not permitted for nivolumab, but were permitted for everolimus.
Permitted and disallowed concomitant medication	Immunosuppressive agents, systemic corticosteroids and any concurrent antineoplastic therapy were prohibited during the study. Live vaccines were to be avoided wherever possible. Patients were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids. Physiologic replacement doses of systemic corticosteroids were permitted, even if >10mg/day prednisone equivalent. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions was permitted. Patients were allowed to continue hormone replacement therapy if initiated prior to randomisation. Bisphosphonates and RANK L inhibitors were allowed for bone metastases if initiated prior to randomisation.

	CheckMate 025
	Supportive care for disease-related symptoms could be offered to all patients on the trial. Palliative (limited-field) radiation therapy and palliative surgical resection was permitted if certain criteria were met.
Primary outcomes	OS: defined as the time from randomisation to the date of death Assessments for survival were performed continuously during treatment and every 3 months during follow-up.
Secondary	ORR: defined as the number of patients with a complete response or a partial response divided by the number of patients who underwent randomisation; PFS: defined as the time from randomisation to first document RECIST-defined tumour progression or death from any cause; Association between OS and tumour expression of PD-L1 (≥1% vs. <1% and ≥5% vs. <5%); Adverse events: graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; HRQL: assessed using the FKSI-DRS questionnaire Disease assessments were performed every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment. Safety assessments were conducted at each clinic visit. HRQL assessments were performed after randomisation and prior to dosing on Day 1 of each cycle beginning with Cycle 2.
Exploratory outcomes	Pharmacokinetic characterisation of nivolumab including exploration of the exposure-response relationship; Immunogenicity characterisation of nivolumab; Biomarker assessment to identify potential predictive biomarkers of efficacy other than PD-L1 expression status; Genetic characterisation to assess the effect of natural variation SNPs in select genes on clinical and safety endpoints; HRQL: assessed using the EQ-5D tool; Health resource utilisation: assessed during the study and at the first two follow-up visits
Pre-planned subgroups	Subgroup analyses assessing the effects of baseline MSKCC risk group (and Heng risk group), number of prior anti-angiogenic therapies, age category, type and duration of prior therapy, number and site of metastases were all pre-planned.

Key: CNS, central nervous system; EQ-5D, EuroQoL 5-Dimension; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; HRQL, health-related quality of life; IV, intravenous; IVRS, interactive voice response system; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, overall response rate; OS, overall survival; PD-L1, programmed death receptor ligand 1; PFS, progression free survival; PS, performance status; RCC, renal cell carcinoma; SNPs, single nucleotide polymorphisms.
Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The hypothesis and associated statistical analysis methods adopted in CheckMate 025 are presented in Table 10.

The all-randomised (intention-to-treat [ITT]) population was the primary population used for the primary efficacy analysis; this included all patients who were randomised to either treatment group in the study.[71, 90] For the safety analyses, the all-treated population was the primary dataset used which comprised all patients who received at least one dose of nivolumab or everolimus. Standard censoring methods were used to take account of missing data in primary OS analysis and secondary PFS analysis.

The final analysis for OS was planned to take place after 569 events had occurred. Interim OS was projected at a 0.0148 nominal significance level; if the results for OS were significant at that level, the study could be stopped at the recommendation of the DMC and declared positive for efficacy. This did occur (see Section 4.3), and thus the interim analysis was considered the final analysis (though patients continue to be followed for survival updates).

Table 10: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CheckMate 025 NCT01668784	Treatment with nivolumab monotherapy will improve overall survival compared to everolimus monotherapy in patients with advanced RCC	OS, PFS and DOR estimated with the use of KM methods. Medians and corresponding 95% CIs were determined with Brookmeyer and Crowley methods; 95% CIs were constructed by means of a log–log transformation. A stratified log-rank test was performed to compare the nivolumab group with the everolimus group with respect to OS and PFS. A stratified HR and CI for nivolumab vs everolimus was obtained by fitting a stratified Cox model with the group variable as a single covariate. The difference in ORR between the nivolumab group and the everolimus group along with the two-sided 95% CI were estimated with the CMH method of weighting, with adjustment for the stratification factors	The sample size was calculated in order to compare the OS between subjects randomised to receive nivolumab and subjects randomised to receive everolimus. The final analysis was planned to take place after 569 events (i.e. deaths). Approximately 569 deaths provides 90% power to detect a HR of 0.76 with an overall type 1 error of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. Approximately 822 subjects were therefore to be randomised to the two arms in a 1:1 ratio. Pre-planned interim analysis was conducted after 398 of the 569 deaths (70%) required for the final analysis	For patients who had not died, OS was censored at last known date alive. For patients who did not progress or die, PFS and DOR was censored on the date of the last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die were to be censored on the date they were randomised.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
			had occurred; the stopping boundary was derived on the basis of the number of deaths with the use of an O'Brien–Fleming alpha-spending function that provided 90% power to detect a hazard ratio of 0.76 with an overall type I error rate of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. The stopping boundaries at interim and final analyses were to be derived based on the number of deaths using O'Brien and Fleming alpha-spending function. It was projected that an observed HR of 0.845 or less, which corresponds to a 2.7 months or greater improvement in median OS (14.8 vs 17.5 months), would result in a statistically significant improvement in OS for	

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
			nivolumab at the final OS analysis.	

Key: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; DOR, duration of response; HR, hazard ratio; KM, Kaplan-Meier; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial.

Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]

4.5 Participant flow in the relevant randomised controlled trials

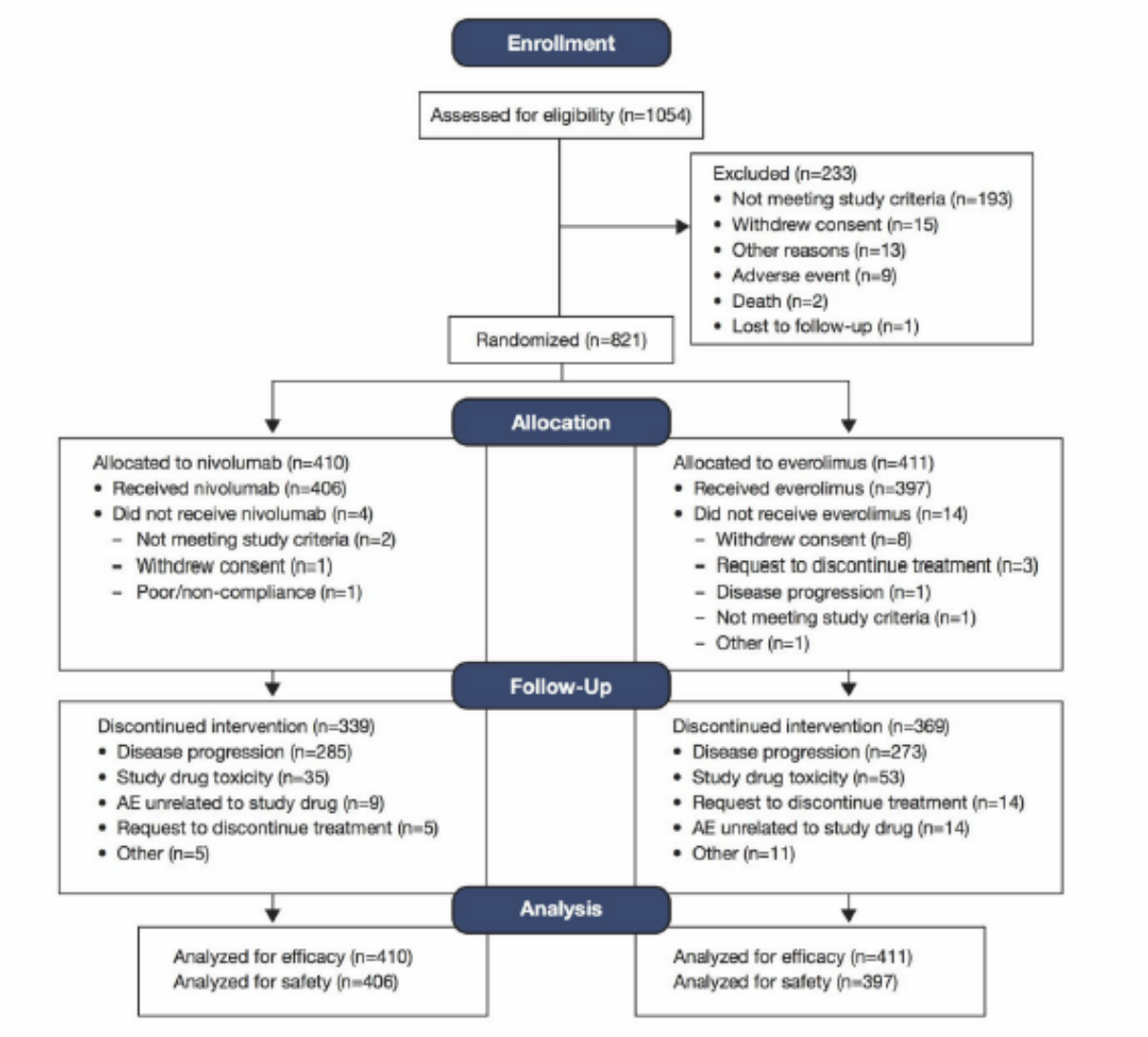
Participant flow

Participant flow for CheckMate 025 is presented as a Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 7.

Of the 821 patients randomly assigned, 803 underwent treatment of which 406 received nivolumab and 397 received everolimus.[71, 90] At data cut off (June 2015), 67 of the 406 patients (17%) in the nivolumab group and 28 of the 397 patients (7%) in the everolimus group continued to receive treatment (for detailed treatment exposure data, see Section 4.12).

The primary reason for treatment discontinuation was disease progression (285 of 406 patients [70%] in the nivolumab group and 273 of 397 patients [69%] in the everolimus group). A lower proportion of patients discontinued study therapy due to study drug toxicity in the nivolumab group compared with the everolimus group (8% versus 13%, respectively).

Figure 7: CONSORT diagram of participant flow in CheckMate 025



Key: AE, adverse event.
Source: Motzer et al. 2015.[90]

Patient characteristics

Baseline demographics and disease characteristics of patients enrolled in CheckMate 025 are presented in Table 11.

The demographics and clinical characteristics of the patients were well balanced between the treatment groups. Among all randomised patients, the median age was 62.0 years (range: 18 to 88) and the majority of patients were white (88%) and male (75%), reflecting the known demographics of this disease.

The majority of patients had received one previous regimen of anti-angiogenic therapy for advanced RCC (72%), with only 28% having received two prior anti-angiogenic therapy regimens. Around two thirds of patients in each group had a poor or intermediate prognostic risk at baseline according to MSKCC risk grouping.

Table 11: Characteristics of participants in CheckMate 025

Baseline characteristic	Nivolumab (n=410)	Everolimus (n=411)
Age, median years (range)	62 (23-88)	62 (18-86)
Gender, male n (%)	315 (77)	304 (74)
Race, Caucasian n (%)	White: 353 (86) Asian: 42 (10) Black: 1 (<1) Other: 14 (3)	White: 367 (89) Asian: 32 (8) Black: 4 (1) Other: 8 (2)
MSKCC risk group, n (%)	Favourable: 145 (35) Intermediate: 201 (49) Poor: 64 (16)	Favourable: 148 (36) Intermediate: 203 (49) Poor: 60 (15)
IMDC risk group, n (%)	Favourable: [redacted] Intermediate: [redacted] Poor: [redacted]	Favourable: [redacted] Intermediate: [redacted] Poor: [redacted]
Karnofsky PS, n (%)	<70: 2 (<1) 70: 22 (5) 80: 110 (27) 90: 150 (37) 100: 126 (31)	<70: 1 (<1) 70: 30 (7) 80: 116 (28) 90: 130 (32) 100: 134 (33)
Common metastasis site, n (%)	Lung: 278 (68) Liver: 100 (24) Bone: 76 (19)	Lung: 273 (66) Liver: 87 (21) Bone: 70 (17)
Previous nephrectomy, n (%)	364 (89)	359 (87)
Time from initial diagnosis to randomisation, median months (range)	31 (1-392)	31 (2-372)
Previous antiangiogenic regimens, n (%)	1: 294 (72) 2: 116 (28)	1: 297 (72) 2: 114 (28)
Previous antiangiogenic therapy, n (%)	Sunitinib: 246 (60) Pazopanib: 119 (29) Axitinib: 51 (12)	Sunitinib: 242 (59) Pazopanib: 131 (32) Axitinib: 50 (12)
Patients with quantifiable PD-L1 expression, n (%):	Yes: 370 (90) No: 40 (10)	Yes: 386 (94) No: 25 (6)

Baseline characteristic	Nivolumab (n=410)	Everolimus (n=411)
PD-L1 expression level, n (%):	≥1%: 94 (25) <1%: 276 (75) ≥5%: 44 (12) <5%: 326 (88)	≥1%: 87 (23) <1%: 299 (77) ≥5%: 41 (11) <5%: 345 (89)
Key: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Centre; PD-L1, programmed death receptor ligand 1; PS, performance status; SD, standard deviation. Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]		

4.6 Quality assessment of the relevant randomised controlled trials

CheckMate 025 was conducted in accordance with good clinical practice (GCP) guidelines by qualified investigators using a single protocol to promote consistency across sites and measures taken to minimise bias.[71, 90]

Baseline demographics and disease characteristics of patients randomised were well balanced, with no key differences between treatment groups. The most common reason for study withdrawal was disease progression, which is accounted for within efficacy assessments. Patient withdrawals for reasons other than disease progression were accounted for with standard censoring methods.

Although this was designed as an open-label trial (due to the distinct differences in administration methods between treatment arms), the primary endpoint of OS is not a subjectively assessed endpoint, and lack of blinding was therefore not thought to have a great effect on the outcome of the study.

Outcome assessments were all conducted in accordance with trial validated methodology. However, in recognition of the limitations of validated RECIST criteria for assessing immunotherapy drugs (see Section 4.3), patients were allowed to receive treatment beyond RECIST-defined progression to better reflect clinical practice.

CheckMate 025 is thought to adequately reflect routine clinical practice in England in respect of population, comparator choice, treatment administration and outcomes being assessed. It is also important to note that alongside clinical efficacy outcomes,

patient reported outcomes (including EuroQol-five dimension [EQ-5D] assessment) were also measured as requested by reimbursement agencies.

Quality assessment in accordance with NICE-recommended checklist for RCT assessment of bias is summarised in Table 12 and presented in full in Appendix 4.

Table 12: Quality assessment results for parallel group RCTs

	CheckMate 025
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
How closely do the RCT(s) reflect routine clinical practice	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England
Key: NHS, National Health Service; RCT, randomised controlled trial. **Source**: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

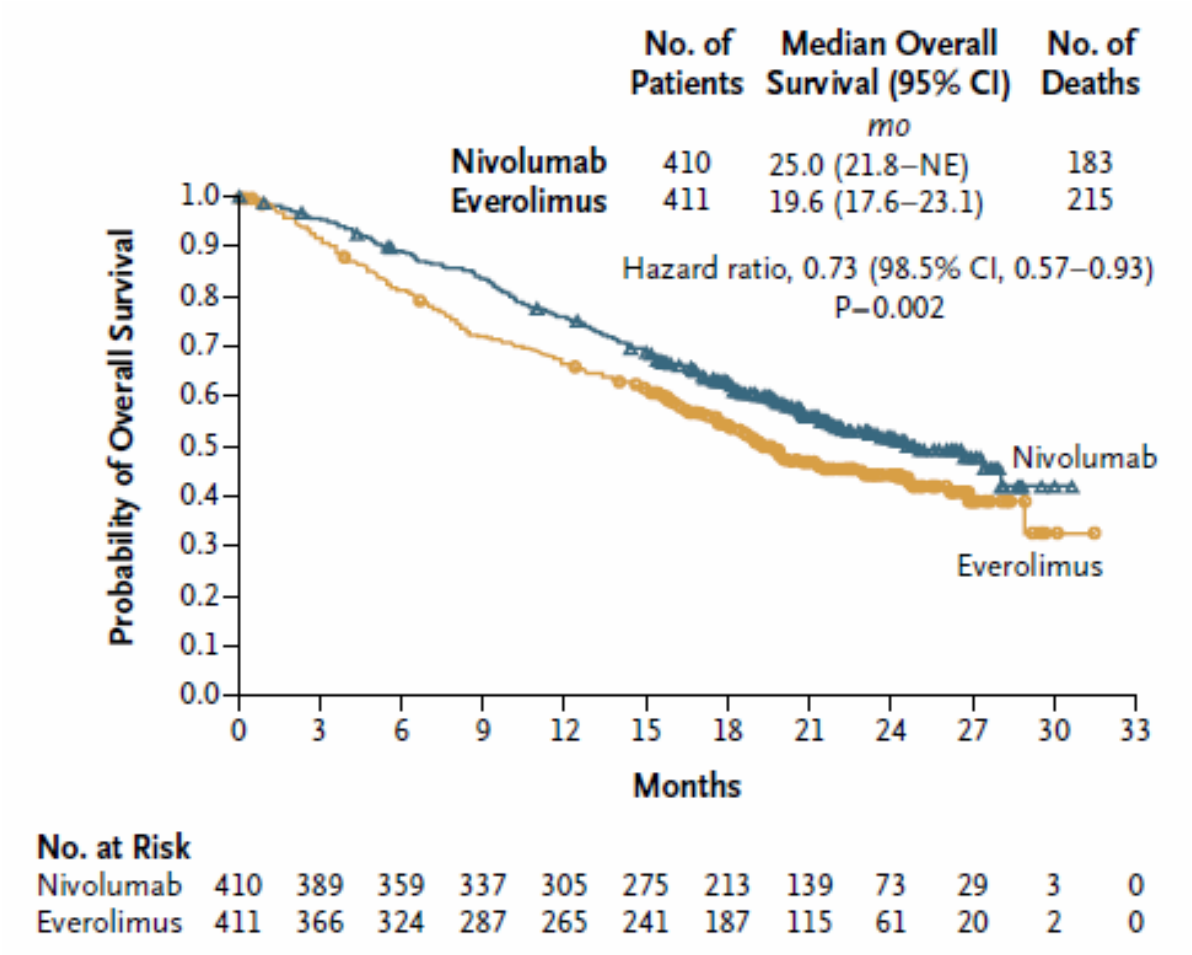
Overall survival (primary endpoint)

With a median follow-up for OS ranging from [redacted] to [redacted] months across treatment groups, median OS was 25.0 months (95% confidence interval [CI]: 21.8 to not

estimable) in the nivolumab group and 19.6 months (95% CI: 17.6 to 23.1) in the everolimus group.[71, 90] The corresponding hazard ratio (HR) for death from any cause confirmed a superior OS benefit with nivolumab compared to everolimus: 0.73 (98.52% CI: 0.57, 0.93); p=0.002.

The Kaplan-Meier (KM) curve for OS is presented in Figure 8.

Figure 8: Kaplan-Meier curve for OS in CheckMate 025, all randomised patients



Key: CI, confidence interval; mo, months; NE, not estimable; OS, overall survival.
Source: Motzer et al. 2015.[90]

Death occurred in 183 of the 410 patients (45%) randomly assigned to receive nivolumab and in 215 of the 411 patients (52%) randomly assigned to receive everolimus. The 6-month survival rate was [redacted] (95% CI: [redacted] to [redacted]) in the nivolumab group and [redacted] (95% CI: [redacted] to [redacted]) in the everolimus group; the 1-

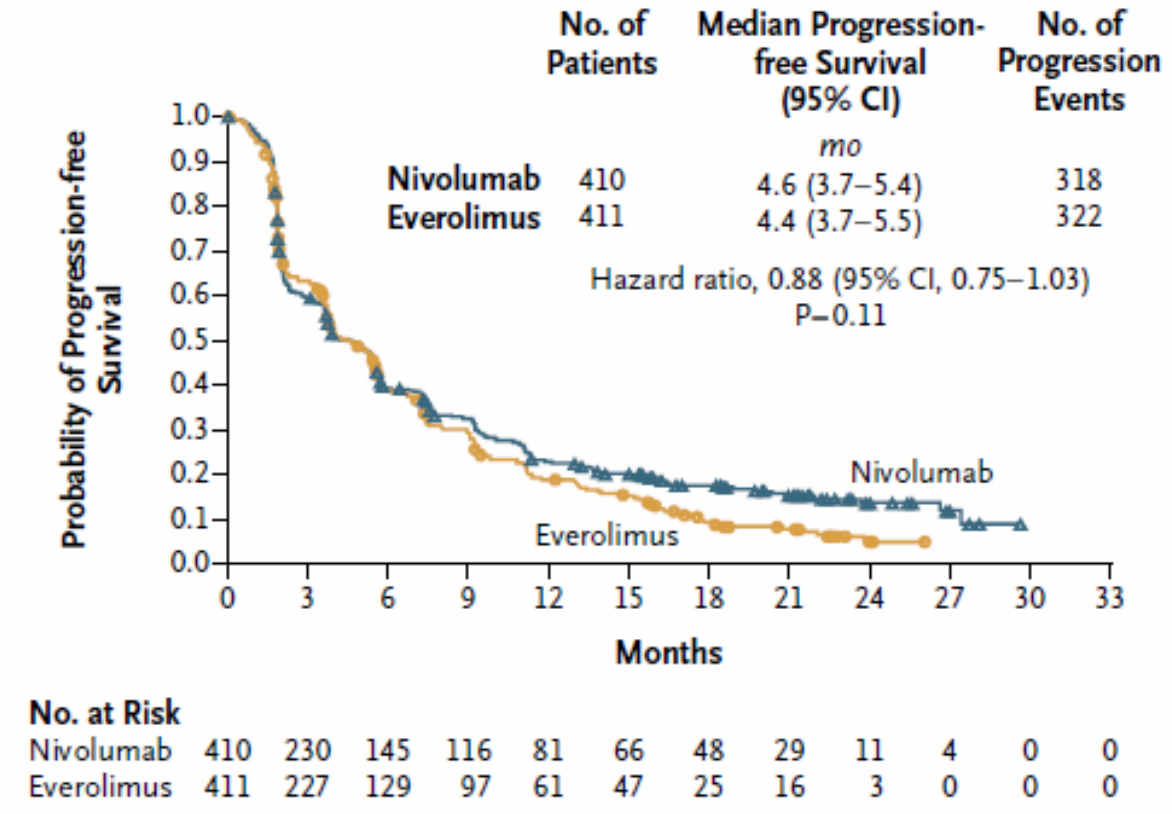
year survival rate for these groups was [redacted] (95% CI: [redacted] to [redacted]) and [redacted] (95% CI: [redacted] to [redacted]), respectively.

Progression-free survival (secondary endpoint)

The median PFS was 4.6 months (95% CI: 3.7 to 5.4) in the nivolumab group and 4.4 months (95% CI: 3.7 to 5.5) in the everolimus group.[71, 90] While not statistically significant, the corresponding HR for death or progression suggests a benefit with nivolumab compared to everolimus: 0.88 (95% CI: 0.75 to 1.03); p=0.11). The 6-month PFS rate was [redacted] in both treatment groups and the 1-year PFS rate was [redacted] in the nivolumab group and 19% in the everolimus group.

The KM curve for PFS is presented in Figure 9.

Figure 9: Kaplan-Meier plot for PFS in CheckMate 025, all randomised patients



Key: CI, confidence interval; mo, months; PFS, progression free survival.
Source: Motzer et al. 2015.[90]

The KM curves overlapped until approximately 6 months, but separated favouring nivolumab beyond this time point and becoming more pronounced over time (when

looking at the tail of the curve). To explore the apparent delayed separation of the curves, an ad hoc sensitivity analysis of PFS in patients who had not had disease progression or died at 6 months (145 patients [35%] in the nivolumab group and 129 patients [31%] in the everolimus group) was performed. The analysis of this subgroup of patients yielded a median PFS of 15.6 months (95% CI: 1.8 to 19.6) in the nivolumab group and 11.7 months (95% CI: 10.9 to 14.7) in the everolimus group (HR: 0.64; 95% CI: 0.47 to 0.88).

It is also important to note that PFS analysis was conducted using RECIST criteria that do not allow for consideration of 'tumour flare', a phenomenon as a result of the immune effect mechanism of action of nivolumab (see Section 2.1). A similar proportion of patients in the nivolumab group (44%) and everolimus group (46%) were treated beyond RECIST-defined progression; however later analyses suggest a higher proportion of patients in the nivolumab group continued treatment for >4 weeks beyond the point of RECIST-defined progression.

Of those in the nivolumab group, [redacted] were considered non-conventional benefiters, defined as patients who had not experienced a best overall response or partial response (PR) or complete response (CR) prior to initial RECIST-defined progression, and met at least 1 of the following criteria:

- Appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of the target lesions ([redacted] patients)
- Initial increase from nadir ≥20% in the sum of the target lesions followed by reduction from baseline of at least 30% ([redacted] patients)
- Initial increase from nadir ≥20% in the sum of the target lesions or appearance of new lesion followed by at least two tumour assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions ([redacted] patients)

Overall survival by PD-L1 expression (secondary endpoint)

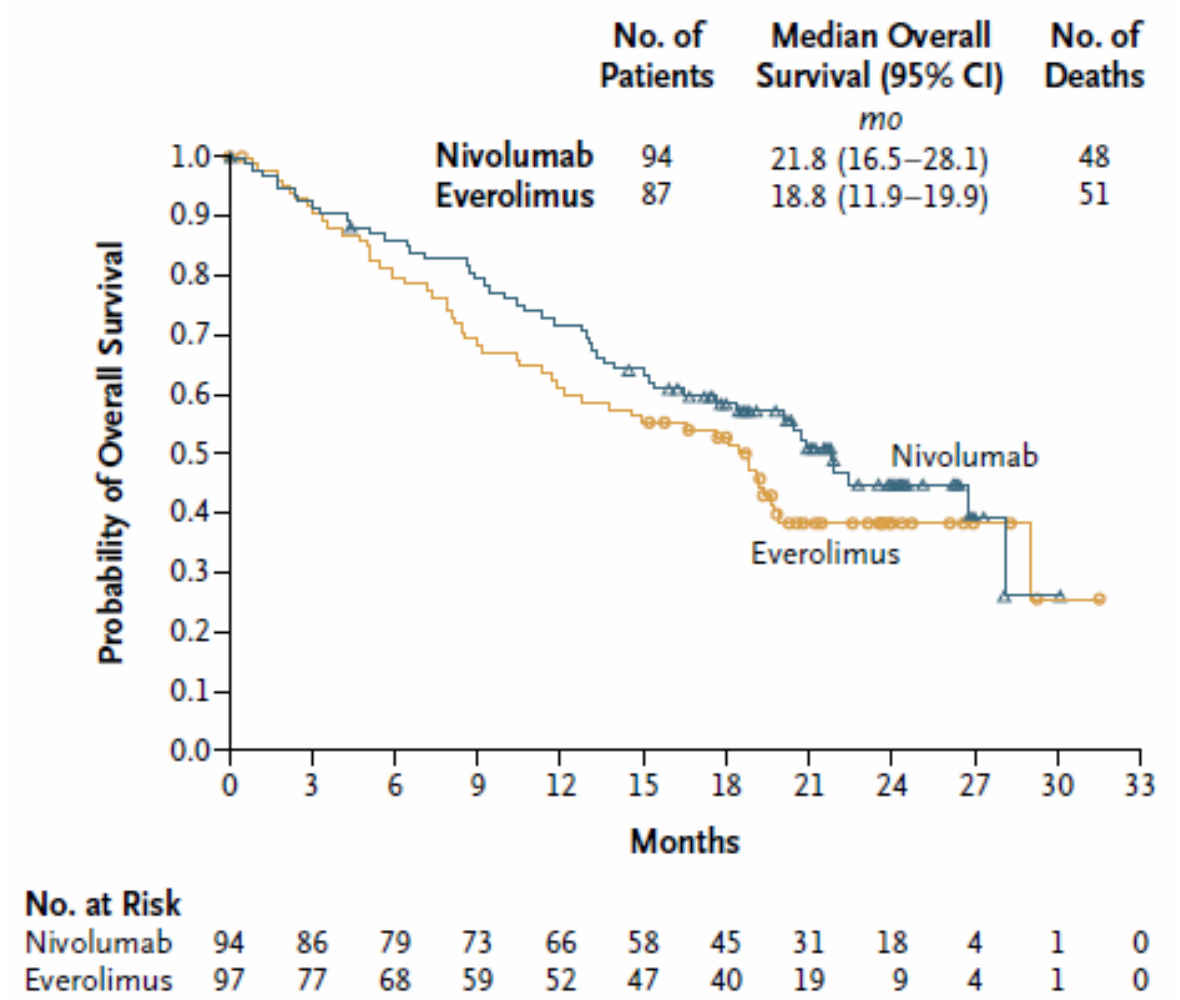
Of the 821 patients who underwent randomisation, 756 had quantifiable tumour PD-L1 expression in pre-treatment samples: 370 patients (90%) in the nivolumab group and 386 patients (94%) in the everolimus group.[71, 90] In total, 181 of the 756 patients

(24%) with quantifiable PD-L1 expression had ≥1% PD-L1 expression, and 575 (76%) had <1% PD-L1 expression at baseline.

Clinically meaningful improvements in OS were observed with nivolumab compared to everolimus regardless of PD-L expression. In patients with pre-study PD-L1 expression ≥1%, median OS was 21.8 months (95% CI: 16.5 to 28.1) for nivolumab patients compared to 18.9 months (95% CI: 11.9 to 19.9) for everolimus patients (HR: 0.77; 95% CI: 0.60, 0.97). In patients with pre-study PD-L1 expression <1%, median OS was 27.4 months (95% CI: 21.4 to not estimable) in the nivolumab group and 21.2 months (95% CI: 17.7 to 26.2) in the everolimus group (HR: 0.77; 95% CI, 0.60 to 0.97).

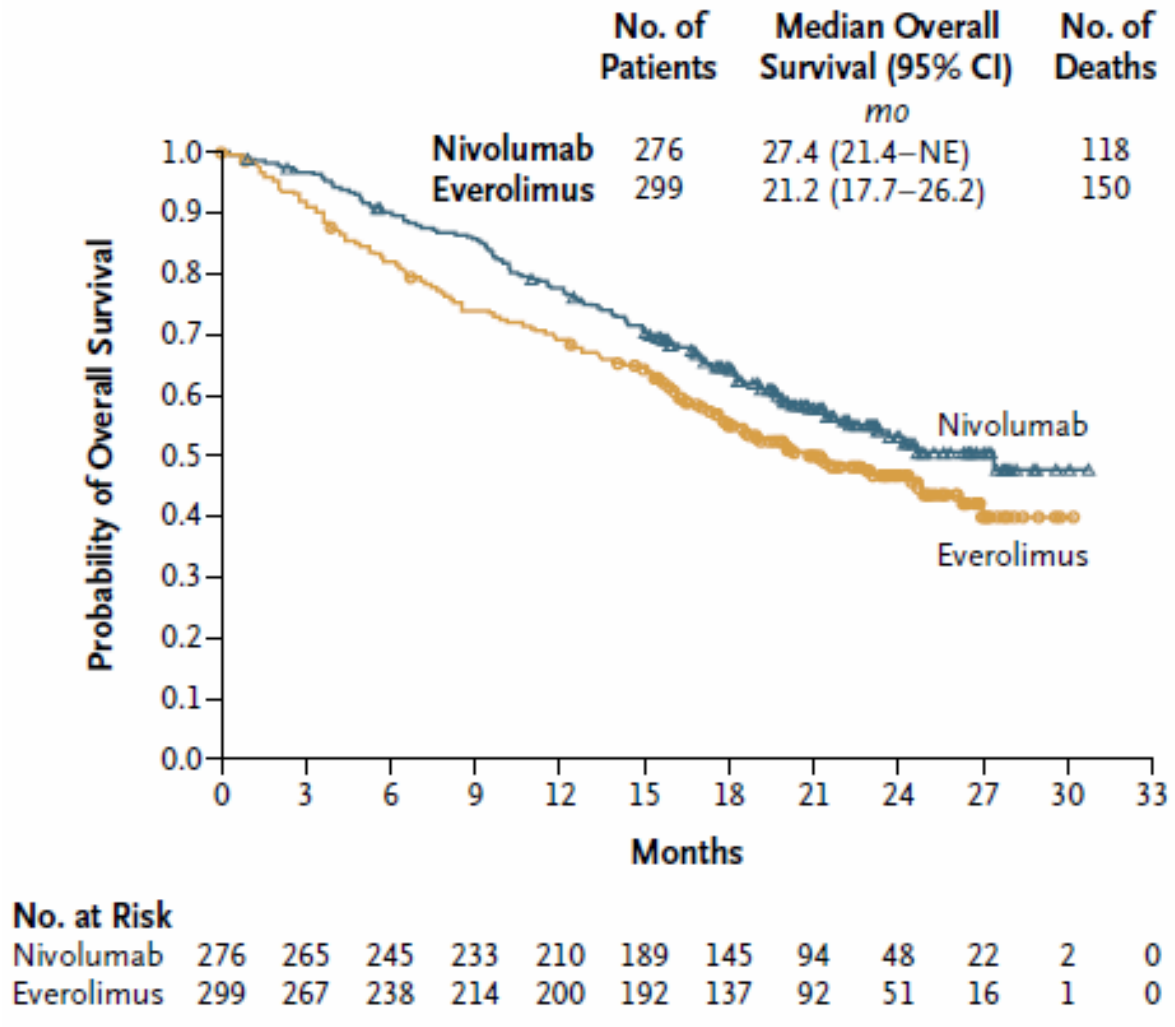
KM plots of OS by PD-L1 expression are provided in Figure 10 and Figure 11.

Figure 10: Kaplan-Meier plot for OS in patients with ≥1% PD-L1 expression



Key: CI, confidence interval; mo, months; OS, overall survival; PD-L1, programmed death receptor ligand 1.
Source: Motzer et al. 2015.[90]

Figure 11: Kaplan-Meier plot for OS in patients with <1% PD-L1 expression



Key: CI, confidence interval; mo, months; NE, not estimable; OS, overall survival; PD-L1, programmed death receptor ligand 1
Source: Motzer et al. 2015.[90]

Similar results were observed among patients with 5% or greater PD-L1 expression as compared with patients with less than 5% PD-L1 expression (data not shown), but interpretation of these data is limited by the small numbers of patients with 5% or greater expression (see Section 4.5).

Objective response rate, time to response and duration of response (secondary endpoints)

In the all randomised population, the investigator-assessed ORR using RECIST was significantly superior in the nivolumab group (25%) compared to the everolimus group (5%) (Odds ratio [OR]: 5.98; 95% CI, 3.68 to 9.72; P<0.001).[71, 90] Complete responses were observed in 4 patients in the nivolumab group and 2 patients in the everolimus group. The ORR with a confirmatory scan after at least 4 weeks (that is, confirmed ORR) was also significantly superior (p<0.001) in the nivolumab group ([redacted]) compared with the everolimus group ([redacted]).

Response analyses are summarised in Table 13.

Table 13: Best overall response per investigator, all randomised patients

	Nivolumab (n=410)	Everolimus (n=411)
ORR, n (%)	103 (25.1)	22 (5.4)
OR (95% CI)	5.98 (3.68-9.72)	
p-value	<0.0001	
Best overall response, n (%)		
CR	4 (1.0)	2 (0.5)
PR	99 (24.1)	20 (4.9)
Median time to response, months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
Median duration of response, months (range)	12.0 (0-27.6)	12.0 (0-22.2)

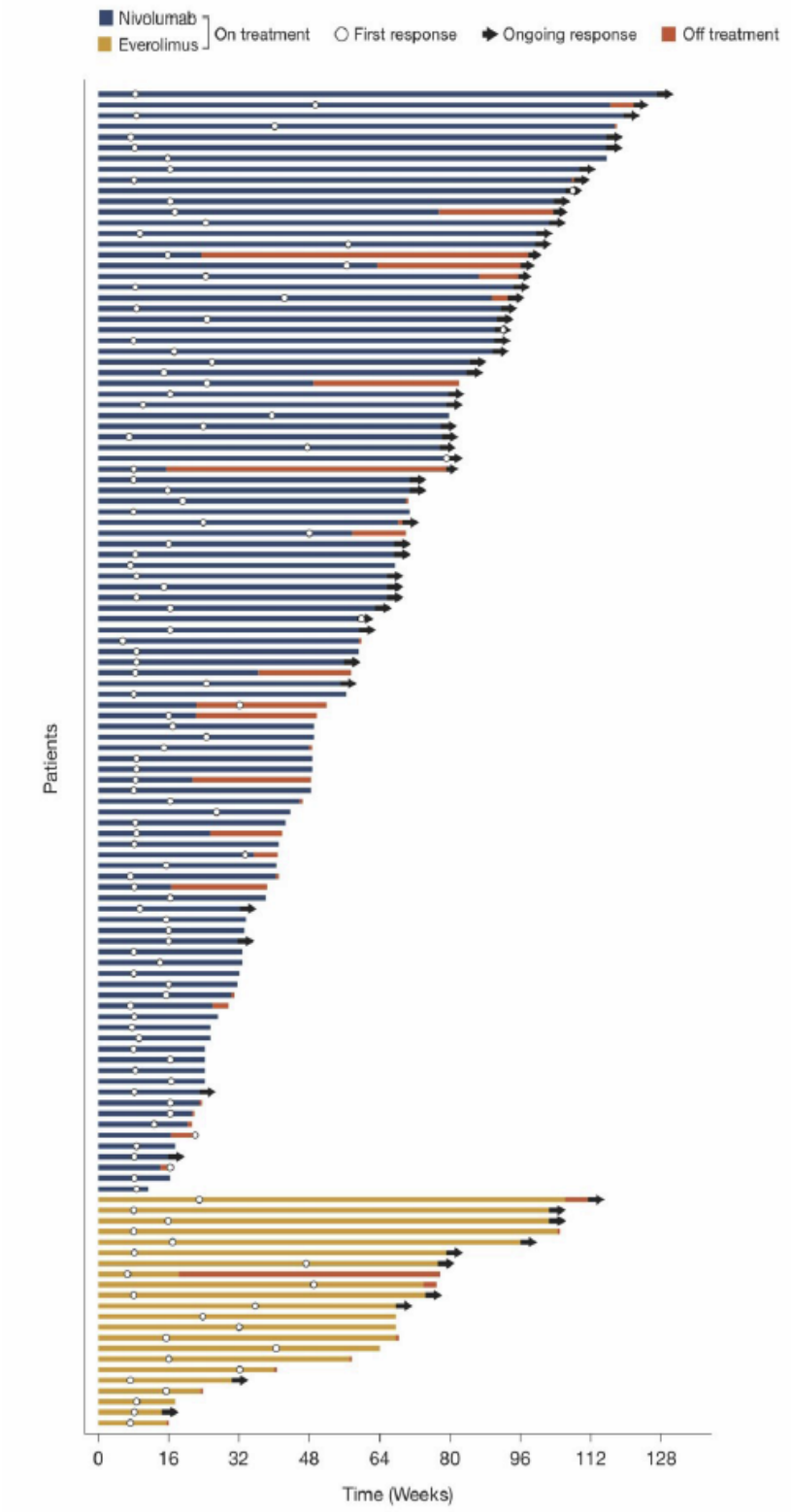
Key: CI, confidence interval; CR, complete response; OR, odds ratio; ORR, objective response rate; PR, partial response.
Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]

The median time to response was similar across both treatment groups and the duration of the response was 12 months for both groups. Among patients who responded to treatment, 48% (49 patients) in the nivolumab group and 46% (10 patients) in the everolimus group had an ongoing response at the time of analysis, as can be seen in the swimmer plot presented in Figure 12; 32 patients (31%) in the nivolumab group and 6 patients (27%) in the everolimus group had an ongoing response for at least 12 months. In patients with confirmed objective response

(n=104), the median duration of response in the nivolumab group was [redacted] months compared with [redacted] months in the everolimus group.

The waterfall plot of response presented in Figure 13 shows the percentage change in tumour burden (assessed as the median change from baseline in the sum of the longest diameters of the target tumour lesions) from baseline for each patient. Reductions in target lesion tumour burden appear to be deeper in the nivolumab group compared to the everolimus group.

Figure 12: Swimmer plot of time to first response and duration of response, all responders



Source: Motzer et al. 2015.[90]

Figure 13: Waterfall plot of best reduction from baseline in sum of diameters of target lesions, all response-evaluable patients

Key: CSR, clinical study report; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
Notes: *Asterisk represents responders as per RECIST criteria; rectangles represent % change truncated to 100%; horizontal dashed line represents a PR according to RECIST criteria (≥30% reduction in tumour size).
Source: CheckMate 025 CSR.[71]

HRQL: FKSI-DRS assessment (secondary endpoint)

The FKSI-DRS is a subscale of the 15-item FKSI (FKSI-15) consisting of nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnoea, cough, fevers and haematuria.[93] Each symptom is rated on a Likert-type scale ranging from 0 to 4, with 0 representing “not at all” and 4 representing “very much”. A summary score is produced by multiplying reversed individual item scores by the number of items in the subscale, divided by the number of items answered. Summary scores range from 0 to 36, with 0 being the worst possible score and 36 being the best possible score.

The FKSI-DRS questionnaire completion rate was 80% or higher throughout the first year of the study.[71, 90] At baseline, the median FKSI-DRS score was 31.0 in both treatment groups. Nivolumab resulted in constant improvement in HRQL, as indicated by increasing FKSI-DRS scores over time. Median changes from baseline in the FKSI-DRS score were significantly greater in the nivolumab group than observed in the everolimus group at each assessment point through Week 104 ($p<0.05$), as presented in Table 14.

Over the course of the study, 55% of patients treated with nivolumab experienced meaningful DRS improvement (defined as ≥2-point increase) compared with 37% of patients treated with everolimus ($p<0.001$). In this subgroup of patients (n=91), improvement in median OS was 8.8 months greater with nivolumab therapy (28.1 months vs 19.3 months); HR for death (95% CI): 0.62 (0.37, 1.06).

Table 14: FKSI-DRS completion rate and median change from baseline

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	Completion rate, %	Median CFB (range)	Completion rate, %	Median CFB (range)	
Baseline	89	-	86	-	-
Week 4	87	0 (-13.0-11.0)	85	-1.0 (-20.0019.0)	<0.001
Week 8	87	0.0 (-13.0–14.0)	85	-1.0 (-19.0016.0)	<0.001
Week 12	85	0.0 (-19.0-17.0)	89	-1.0 (-18.0-19.0)	<0.001
Week 16	86	0.0 (-16.0-13.0)	89	-1.0 (-17.0-16.0)	<0.001
Week 20	86	0.0 (-11.0-16.0)	89	-1.0 (-16.0-16.0)	<0.001
Week 24	86	0.0 (-10.0-15.0)	87	-1.0 (-13.0-16.)	<0.001
Week 28	86	0.0 (-9.0-12.0)	88	-1.0 (-13.0-14.0)	<0.001
Week 32	88	1.0 (-9.0-15.0)	81	-1.0 (-11.0-15.0)	<0.001
Week 36	84	1.0 (-15.0-18.0)	85	-1.0 (-11.0-15.0	<0.001
Week 40	83	1.0 (-11.0-11.0)	84	-1.0 (-12.0-20.0)	<0.001
Week 44	83	1.0 (-11.0-16.0)	79	-1.0 (-10.0-18.0)	<0.001
Week 48	84	1.0 (-9.0-17.0)	81	-1.0 (-12.0-25.0)	<0.001
Week 52	80	1.0 (-9.0-17.0)	81	0.0 (-10.0-20.0)	<0.001
Week 56	81	1.0 (-7.0-17.0)	80	-1.0 (-17.0-17.0)	<0.001
Week 60	84	1.0 (-10.0-17.0)	79	-1.0 (-10.0-20.0)	<0.001
Week 64	78	1.0 (-9.0-16.0)	76	-1.0 (-8.0-12.0)	<0.001
Week 68	77	2.0 (-7.0-18.0)	73	-1.0 (-10.0-22.0)	<0.001
Week 72	76	1.0 (-6.0-16.0)	71	0.0 (-10.0-9.0)	0.001
Week 76	77	1.0 (-9.0-16.0)	76	0.0 (-10.0-19.0)	0.011
Week 80	76	2.0 (-5.0-11.0)	73	-1.0 (-10.0-25.0)	0.003
Week 84	74	1.5 (-6.0-16.0)	75	0.0 (-15.0-24.0)	0.002
Week 88	80	2.0 (-6.0-16.0)	65	0.0 (-12.0-22.0)	0.005
Week 92	71	3.0 (-4.0-18.0)	60	-1.0 (-12.0-21.0)	0.012
Week 96	81	2.0 (-1.0-7.0)	63	-2.5 (-12.0-20.0)	0.003
Week 100	79	3.0 (-2.0-10.0)	64	-3.0 (-12.0-12.0)	0.002
Week 104	77	2.0 (-1.0-16.0)	90	-2.0 (-7.0-15.0)	0.019

Key: CFB, change from baseline.
Notes: [a], between-group comparison for median change from baseline
Source: Motzer et al. 2015.[90]

HRQL: EQ-5D assessment (exploratory endpoint)

EQ-5D data was also captured within the CheckMate 025 trial in recognition of its preferred use in economic modelling (see Section 5.4). Descriptive data for this exploratory endpoint is presented in Appendix 6.

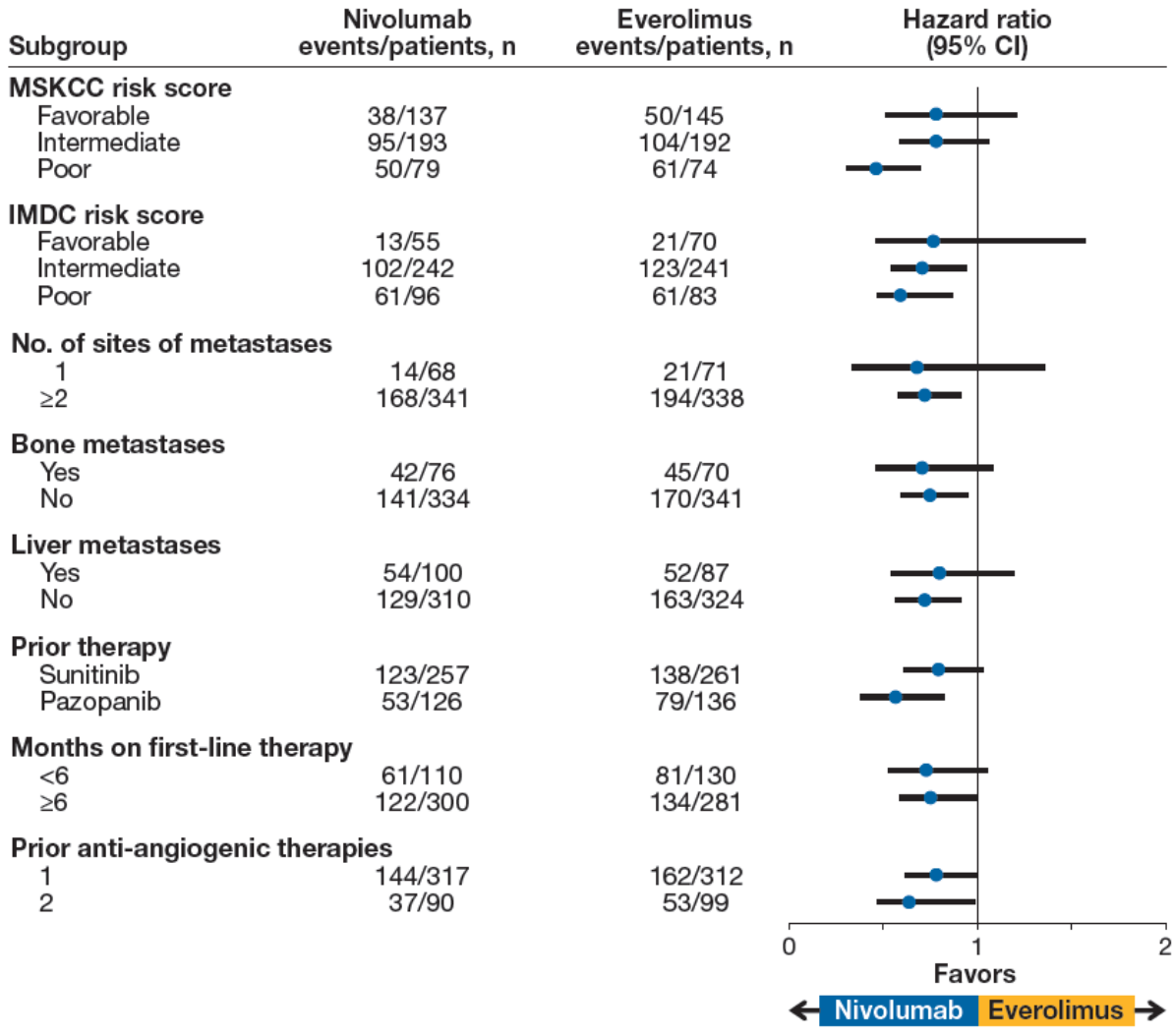
In summary, a significant difference in EQ-5D visual analogue scale (VAS) between treatment groups were observed from weeks 4 through 68, weeks 76 through 80, and weeks 88 through 92. Over the course of the study, 53% of patients treated with nivolumab experienced meaningful EQ-5D VAS improvement (defined as ≥7-point increase) compared with 39% of patients treated with everolimus (p=0.005).

The EQ-5D utility index showed significant benefit with nivolumab from weeks 8 through 12, weeks 24 through 44, weeks 52 through 68 and week 80.

4.8 Subgroup analysis

Analysis in pre-specified subgroups showed consistently greater OS for nivolumab treated patients as compared to everolimus treated patients.[71, 91] Importantly, subgroup analyses demonstrated OS benefit with nivolumab, irrespective of baseline prognostic risk group and prior treatment history, as depicted in Figure 14. Particularly remarkable benefit (given their baseline prognosis) was observed in patients with a poor MSKCC risk score (HR [95% CI]: 0.48 [0.32, 0.70]).

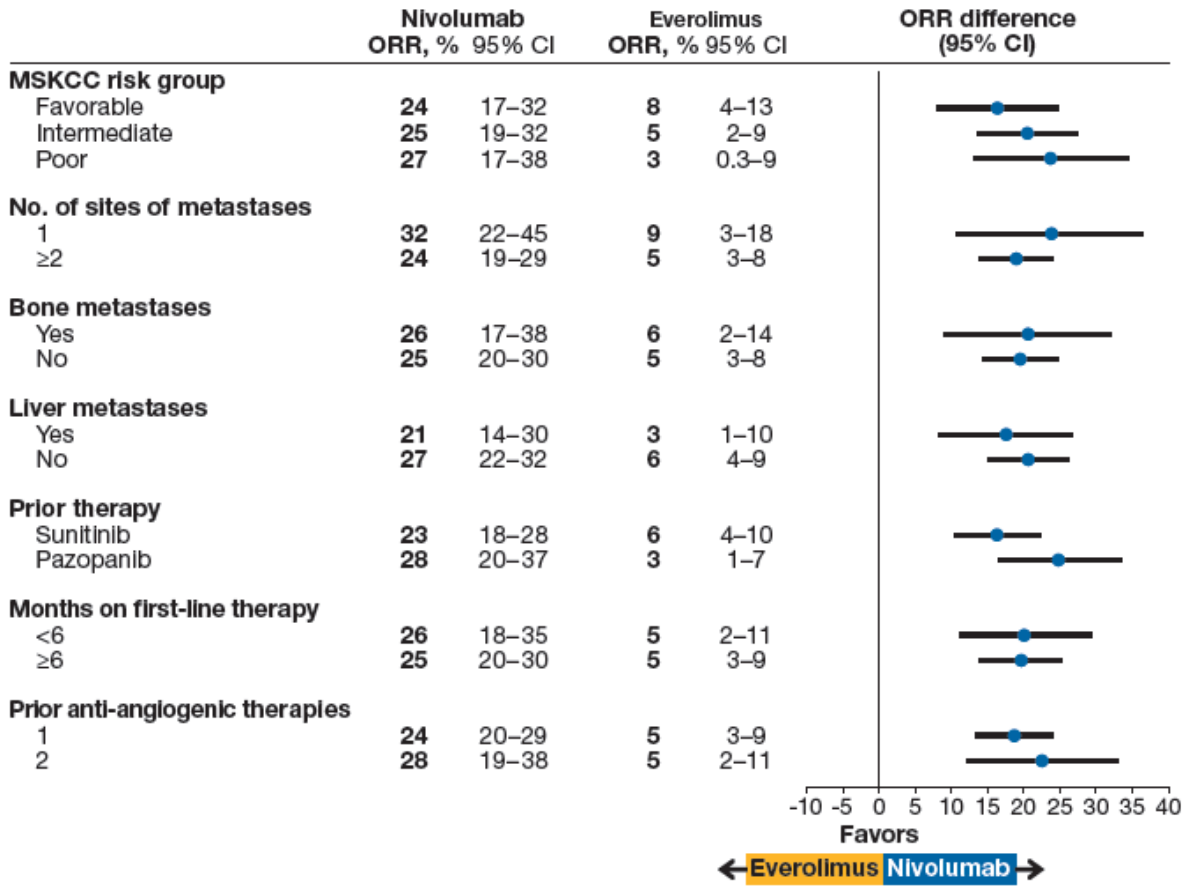
Figure 14: Forest plot of treatment effect on OS in key subgroups



Key: CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival.
Source: Motzer et al. 2016.[91]

Subgroup analyses of ORR also demonstrated consistently greater ORR for nivolumab treatment patients, as presented in Figure 15.

Figure 15: Forest plot of treatment effect on ORR in key subgroups



Key: CI, confidence interval; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate.
Source: Motzer et al. 2016.[91]

4.9 Meta-analysis

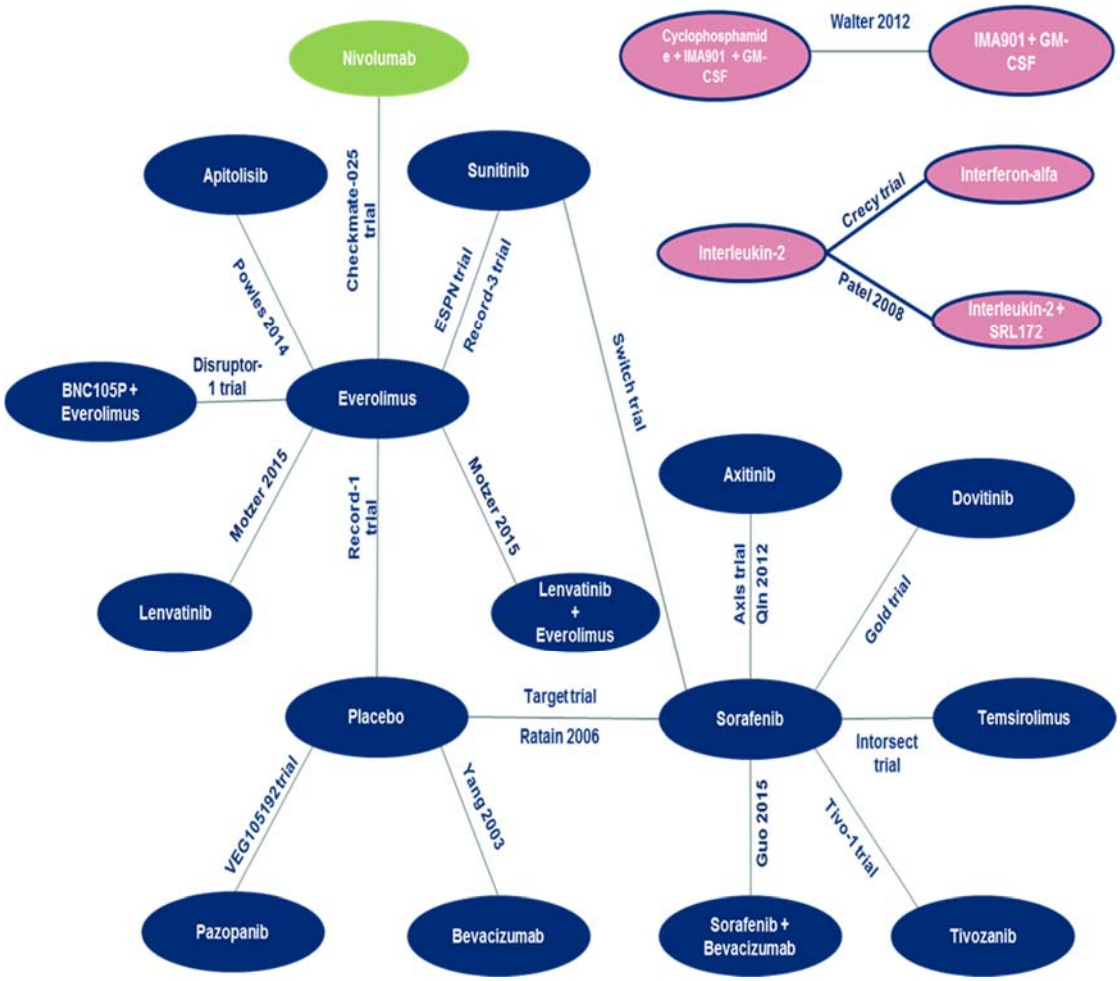
Meta-analysis has not been performed because a single RCT provides evidence supporting the use of nivolumab 3mg/kg monotherapy for the treatment of advanced RCC. Details of this study (CheckMate 025) are presented in Sections 4.3 to 4.8.

4.10 Indirect and mixed treatment comparisons

4.10.1 Study selection

The systematic literature review methods used to identify trials for potential inclusion in a NMA are described in Section 4.1. In addition to the CheckMate 025 trial, 21 RCTs met the eligibility criteria (Table 15) and 18 trials (including CheckMate 025) could be connected within an evidence network, as presented in Figure 16.

Figure 16: Master evidence network for potential indirect treatment comparison



A feasibility assessment for a potential NMA with CheckMate 025 was conducted with outcomes of interest pre-defined as key efficacy outcomes of relevance to patients and healthcare providers (OS and PFS). Potential sources of bias or

heterogeneity (compared with CheckMate 025) were also evaluated within this feasibility assessment; these conclusions are summarised in Table 15.

Table 15: Feasibility assessment of RCTs contributing to the identified evidence base for potential NMA with CheckMate 025

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
AXIS[50, 68]	This was a randomised, large sample size (>500) study. This study directly compared two VEGFR TKIs, axitinib and sorafenib. The study was conducted in multiple countries across the globe. This was an open label trial, but endpoints were adjudicated by masked independent radiology review.	The study recruited 33% patients in MSKCC poor risk group, which was the highest proportion of such patients recruited across the included studies.	Included in NMA: OS PFS
DISRUPTOR-1[73]	This was a randomised, moderate sample size (>100) study.	It is published as a conference abstract with limited information. Baseline demographic and clinical characteristics were not reported for comparability.	Not included due to limited data availability.
ESPN[74]	-	This trial is the only trial that is evaluating non-clear renal cell carcinoma patients. The study evaluated a small sample size (<100). Baseline demographic and clinical characteristics were not reported for comparability. The blinding details for the study were not available.	Not included due to non-clear cell patients, small sample size and limited data availability.

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
GOLD[75]	This was a randomised, large sample size (>500) study. Method of randomisation was adequate (IVRS). This was an open label trial, but endpoints were adjudicated by central radiology review. Baseline demographic and clinical characteristics were comparable with other studies.	>90% of patients had received two lines of prior therapy (1 prior VEGF targeted therapy and 1 prior mTOR inhibitor therapy), which was the highest proportion of such patients recruited across the included studies.	Included in NMA: OS PFS
Guo et al. 2015[76]	It was active controlled randomised controlled trial.	It is published as a conference abstract with limited information. Baseline demographic and clinical characteristics were not reported for comparability. The study evaluated a small sample size (<100). Enrolled 100% Asian patients.	Not included due to small sample size and limited data availability.
INTORSECT[77]	This was a randomised, large sample size (>500) study. Method of randomisation was adequate (Computerised central randomisation system). This was an open label trial, but endpoints were adjudicated by independent review committee.		Included in NMA: OS PFS

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
	Baseline demographic and clinical characteristics were comparable with other studies.		
Motzer et al. 2015[78]	This was a randomised, moderate sample size (>100) study.	It is published as a conference abstract with limited information. Baseline demographic and clinical characteristics were not reported for comparability. Phase II study.	Not included due to limited data availability.
Powles et al. 2014[80]	-	It is published as a conference abstract with limited information. Baseline demographic and clinical characteristics were not reported for comparability. The study evaluated a small sample size (<100). The blinding details for the study were not available. Phase II study.	Not included due to small sample size and limited data availability.
Qin et al. 2012[81]	This was a randomised, moderate sample size (>100) study. This was an open label trial, but endpoints were adjudicated by independent review committee.	It is published as a conference abstract with limited information. Baseline demographic and clinical characteristics were not reported for comparability. Enrolled 100% Asian patients.	Not included due to limited data availability.

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
Ratain et al. 2006[82]	This was a double-blind study. Method of generating randomisation was adequate (IVRS).	The study evaluated small sample size study (<100).	Not included due to small sample size.
RECORD-1[51, 70]	This is the only study connecting CheckMate 025 to other trials in the potential network for OS analysis. Therefore, this study would be required to connect nivolumab and other interventions and hence will be a part of the relevant network. This was a randomised, active-controlled, large sample size (>400) study conducted in multiple countries. Method of randomisation was adequate (Centrally via validated computer system). This was a double-blind study. Baseline demographic and clinical characteristics were largely comparable with other studies.	Cross-over trial design such that subsequent OS analysis based on ITT population are likely to be confounded.	Included in NMA: OS PFS
RECORD-3[83]	This was a randomised, moderate sample size (>100) study. Baseline characteristics were separately reported for second-line treated patients.	Sequential trial design such that randomisation was for first-line treatment. Efficacy data only reported for first-line or combined treatment. Phase II trial.	Not included due to sequential trial design.
SWITCH[84]	-	It is published as a conference abstract with limited information.	Not included due to limited data availability.

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
		Baseline demographic and clinical characteristics were not reported for comparability. Sequential trial design such that randomisation was for first-line treatment. Efficacy data only reported for first-line or combined treatment.	
TARGET[85, 94]	This was a randomised, large sample size study enrolling the highest number of patients (903) across all the included studies. This was a double-blind study.	This was the only study where percentage of patients with poor MSKCC score were zero, which is different from the rest of the studies in the evidence network. Prior VEGF pathway inhibitor therapy not permitted. Cross-over trial design with basic censoring methods used to adjust HR for OS analysis.	Included in NMA: OS PFS
TIVO-1[86]	This was a randomised, moderate sample size (>100) study. This was an open label trial, but endpoints were adjudicated by independent radiology review. The overall baseline demographic and disease characteristics are comparable with other studies.	Mixed patient population (treatment naïve and treatment exposed). Baseline demographic and clinical characteristics were not separately reported for prior treated patients. Overall baseline characteristics reported both for pre-treated and naïve has been evaluated for comparability. Prior VEGF-targeted therapy and mTOR inhibitor therapy were not permitted. The publication does not specify how OS data from patients who have crossed over	Included in NMA: PFS Not included in OS NMA due to trial crossover and limited information on how this was handled.

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
		from either arm has been handled. It is described that patients were to be recruited to a separate protocol upon crossover and it is unclear how the sponsor derived the results for subsequent OS. Furthermore, imbalances in the crossover design may have compromised the OS outcome.	
VEG105192[87, 95]	This was a randomised, moderate sample size (>100) study. Method of randomisation was adequate (Computerised central randomisation system). This was a double-blind study. The overall baseline demographic and disease characteristics are comparable with other studies.	Mixed patient population (treatment naïve and treatment exposed). Baseline demographic and clinical characteristics were not separately reported for prior treated patients. Overall baseline characteristics reported both for pre-treated and naïve has been used for comparability assessment. Prior therapy cytokine-based. Cross-over trial design with censor weighting used to adjust HR for OS analysis.	Included in NMA: OS PFS
Yang et al. 2003[89]	This was a randomised, moderate sample size (>100) study. This was a double-blind study. The majority of patients had ECOG PS 0 (78%) - comparable with other studies.	Data for other baseline disease characteristics were not reported. Phase II study. Prior therapy cytokine-based Cross-over trial design such that OS results based on ITT population are likely to be confounded.	Included in NMA: OS PFS

	Key methodological and clinical parameters assessed for potential sources of bias or heterogeneity		
	Parameters supporting inclusion of study	**Parameters supporting exclusion of study**	**Outcome**
Key: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; IVRS, interactive voice response system; MSKCC, Memorial Sloan Kettering Cancer Center; mTOR, mammalian target of rapamycin; NMA, network meta-analyses; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.			

The studies included in the final evidence base utilised for the NMA are summarised in Table 16. The primary reason for study exclusion from the NMA was small sample size and/or limited data availability due to study results only being available from conference abstracts at the time of assessment (Table 15). Additional methodological details and key patient characteristics are provided in Appendix 5, along with a quality assessment of included studies.

It is important to note that while these studies were considered comparable to a basic level required for ITC, there are a number of key differences between included trials that may mean some caution is warranted when interpreting the results, such as: differences in patient populations including baseline risk and treatment history; differences in trial designs, particularly in regard to primary efficacy outcome(s); and differences in post-progression treatment options with patients enrolled in more recent trials having access to potentially superior subsequent therapy. These are discussed further as part of the results presentation.

Table 16: Studies included in the final evidence base for indirect treatment comparison

Trial name	Design	Population	Sample size	Treatment arms	Primary endpoint
AXIS[68]	RCT Phase III Double-blind Parallel group	Adult patients with clear-cell mRCC who had progressed despite first-line systemic therapy (sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines).	723	Axitinib Sorafenib	PFS
GOLD[75]	RCT Phase III Open-label Parallel group	Adult patients with clear-cell mRCC who had received one previous VEGF-targeted therapy and one previous mTOR inhibitor.	570	Dovitinib Sorafenib	PFS
INTORSECT[77]	RCT Phase III Open-label Parallel group	Adult patients with mRCC who had documentation of progressive disease while receiving first-line sunitinib.	512	Temsirolimus Sorafenib	PFS
RECORD-1[51]	RCT Phase III Double-blind Cross-over	Adult patients with clear-cell mRCC who had documentation of progressive disease during or within 6 months of stopping sunitinib and/or sorafenib (prior therapy with cytokines and/or VEGF inhibitors also permitted).	416	Everolimus Placebo	PFS
RECORD-3[83]	RCT Phase II Open-label Sequencing	Adult patients with mRCC who had not received prior systemic therapy.	471[a]	Everolimus-sunitinib Sunitinib-everolimus	PFS
TARGET[85]	RCT Phase III	Adult patients with clear-cell mRCC which had progressed after one systemic treatment within	903	Sorafenib	OS

Trial name	Design	Population	Sample size	Treatment arms	Primary endpoint
	Double-blind Cross-over	the previous 8 months (not including VEGF pathway inhibitors).		Placebo	
TIVO-1[86]	RCT Phase III Open-label Parallel group	Adult patients with clear-cell mRCC who had prior nephrectomy and 0-1 prior therapies for mRCC (not including VEGF-targeted or mTOR inhibitor therapy).	154[b]	Tivozanib Sorafenib	PFS
VEG105192[87]	RCT Phase III Double-blind Cross-over	Adult patients with advanced and/or metastatic RCC who were treatment-naïve or had received one prior cytokine-based systemic therapy.	202[b]	Pazopanib Placebo	PFS
Yang et al. 2003[89]	RCT Phase II Double-blind Cross-over	Adult patients with clear-cell mRCC and documented progression of disease despite prior therapy (including IL-2 unless contraindicated to standard IL-2).	116	Bevacizumab 10mg Bevacizumab 3mg Placebo	ORR; TTP
Key: IL-2, interleukin mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TTP, time-to-progression; VEGF, vascular endothelial growth factor. **Notes**: [a], treatment naïve patients randomised to first-line treatment; [b], pre-treated subgroup of interest.					

4.10.2 Network meta-analysis

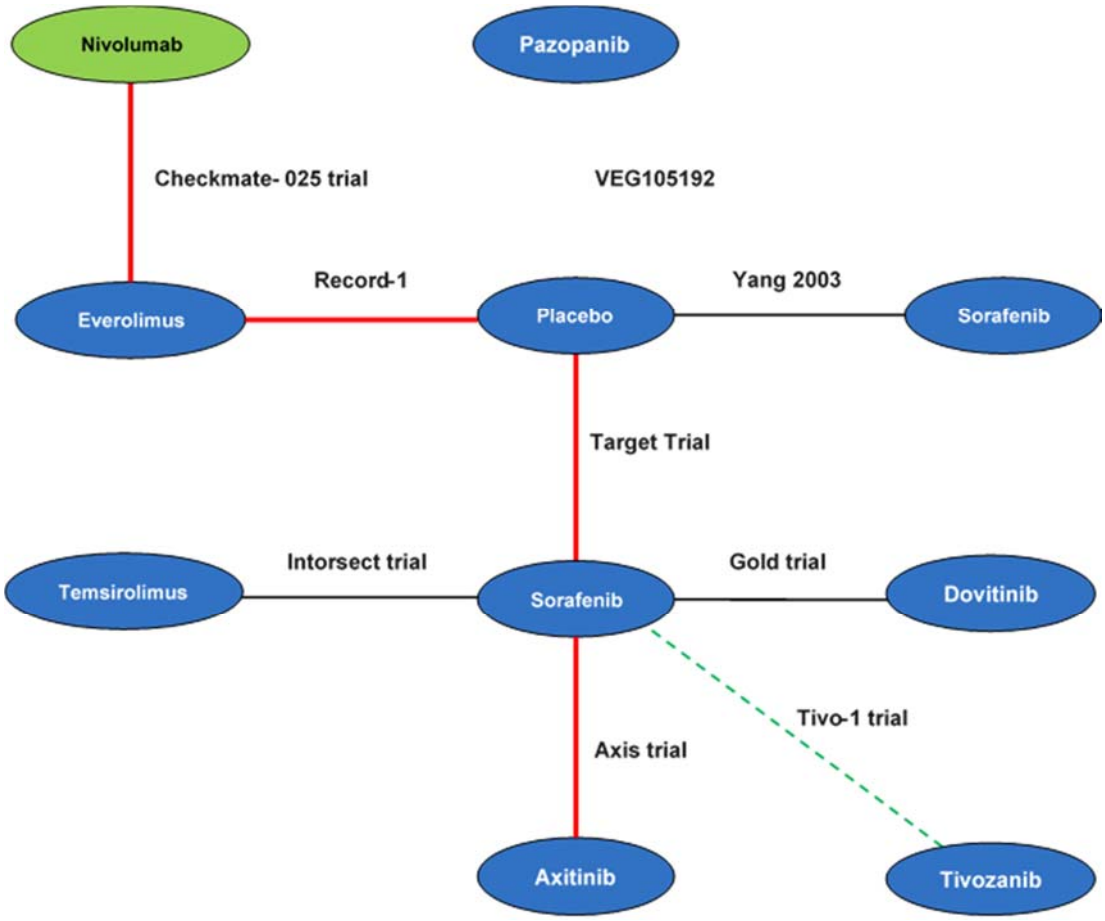
In addition to everolimus for which direct head-to-head data are available, the key comparisons of interest to the decision problem are nivolumab versus axitinib and nivolumab versus BSC, as no head-to-head data are available for these comparisons. In the absence of a common comparator between key trials of nivolumab and axitinib therapy, a NMA that maximises information across the evidence network was considered to be the most appropriate methodology to allow indirect comparison to both key comparisons. For the purpose of this appraisal, placebo from the TARGET[85] and RECORD-1[51] trials has been used as a proxy for BSC.

Clinical efficacy

The NMA results presented in this section focus on two key efficacy endpoints: OS and PFS. These represent key outcomes of interest to clinicians and patients and are consistently selected as the primary and secondary efficacy endpoints in RCC trials. The NMAs for these efficacy endpoints are utilised in health economic modelling (see Section 5).

The final evidence network utilised for the NMA of OS data is presented in Figure 17. The section of the network directly relevant to the decision problem of interest is highlighted in red; allowing comparisons of nivolumab to everolimus, axitinib and placebo. The green dashed line indicates inclusion of the TIVO-1 trial for the PFS analysis only.

Figure 17: Evidence network for meta-analysis



Notes: Bevacizumab doses of 3 mg and 10 mg q2w have been combined. Data from the TIVO-1 trial is included in the synthesis of PFS but not OS (represented by green dotted line).

4.10.3 Methods and outcomes of included studies

An NMA has been conducted on the log-hazard ratio scale, which is a relative measure of treatment efficacy. The key assumption of this analysis is that of intra-trial proportional hazards; survival curves do not cross and are related to each other through a constant, time invariant, exponent. Use of this relative measure of treatment efficacy avoids the need for patients recruited to different trials within the network to have, on average, the same prognosis e.g. if there are multiple placebo arms in a trial, these patients do not have to show the same median overall survival. However, the magnitude of treatment effects observed is assumed to be constant across the patient populations recruited to the trials within the network.

Analyses have been conducted using the R package 'netmeta'.[96] The package utilises graph theoretical methods in a frequentist framework to analysis data from treatment networks.[97] The package is referenced in the NMA toolkit provided on the Cochrane website.[98] The code for the NMA has been supplied separately.

Fixed effects models have been presented as there is only one trial comparing the same two treatments and, therefore, the estimation of between trial heterogeneity is confounded with the estimation of treatment effect. As such, it is not possible to investigate measures of statistical heterogeneity within this treatment network. Furthermore, when random effects model were estimated, they gave identical results to the fixed effects models.

Two different sets of analyses have been performed for OS. The first uses the ITT hazard ratios available for each of the trials; this used survival data from all randomised patients as was observed in each of the trials irrespective of subsequent treatment received. The second uses, where available, hazard ratios that are crossover adjusted/crossover free.

As described in Section 4.7, the KM curves for PFS within Checkmate-025 overlapped until approximately 6 months, but separated favouring nivolumab beyond this time point, becoming more pronounced over time. This is likely the result of nivolumab's unique mode of action and the high proportion of patients treated beyond progression in CheckMate 025. The use of the HR to describe the treatment effect between nivolumab and everolimus for PFS is therefore limited (the HR assumes that the treatment effect is constant over time) and results for this outcome should be interpreted with caution. A visual inspection of the KM curves for the AXIS, RECORD-1 and Target trials suggests that proportional hazards do hold for these trials. Indeed, for the single technology appraisal of axitinib in RCC (TA333), proportional hazards were assumed when analysing a similar network (axitinib for treating advanced RCC after failure of prior systemic treatment).[99] As a result, all treatments in the NMA will be compared against both nivolumab and everolimus; comparisons against everolimus will allow different scenarios to be explored when modelling the treatment effects of nivolumab within the economic model.

It is also important to note that although proportional hazards have been observed between nivolumab and everolimus for OS within the time frame of Checkmate-025,

nivolumab has demonstrated an immune-response OS tail in melanoma patients (NICE ID845), and the absence of such a tail in the RCC evidence may be due to insufficient follow-up and patient numbers that were not powered to find such an effect. This was voiced at clinical consultation, as described in Sections 5.3 and 5.10, and is considered to be of specific importance because the immunotherapy mode of action of nivolumab is unique within the network; it has key differences when compared to standard anti-cancer therapies.

As proportionality holds for OS within CheckMate-025, the OS results presented in this section will focus on the comparison against nivolumab; for PFS, the description will focus on the comparison against both nivolumab and everolimus.

4.10.4 Evidence base for overall survival

Figure 17 presents the treatment network for OS. Table 17 presents the ITT and crossover adjusted/free hazard ratio and 95% CI of the trials contributing to the network meta-analysis of OS.

Four of the eight studies contributing to the evidence network for OS reported crossover of treatments following disease progression.[51, 85, 87, 89] Of specific focus for this decision problem are the TARGET, AXIS and RECORD-1 trials [51, 68, 85]; these trials provide key links to make comparisons for nivolumab with everolimus, placebo and axitinib.

The TARGET trial permitted crossover from placebo to sorafenib following a statistically significant PFS benefit being observed (assessed in May 2005). [85] Although, at this point, the OS data were relatively immature (220 deaths; 41% of the protocol defined 540 deaths had been observed), the estimation of survival was unbiased and there was a numerical advantage of sorafenib over placebo (HR = 0.72; 95% CI; 0.54 to 0.94; P = 0.02). The analysis did not reach the pre-specified O'Brien–Fleming boundaries for statistical significance. In the final analysis of the ITT population, 16 months after crossover from placebo to sorafenib was permitted (September 2006), survival in the sorafenib group again did not reach the boundary for statistical significance (HR=0.88; 95% CI, 0.74, 1.04; P = 0.146). In order to explore the uncertainty in the estimation of relative efficacy between sorafenib and placebo, both these hazard ratios will be used in the network meta-analysis; 0.88

(95% CI, 0.74, 1.04) within the ITT network and 0.72 (95% CI; 0.54, 0.94) within the crossover adjusted network.

Using data from the RECORD-1 trial, Korhonen et al. attempted to adjust for treatment crossover using a rank-preserving structural failure time (RPSFT) model.[100] When the RPSFT methodology was applied to the data from RECORD-1, the HR (95% CI) reduced from 0.87 (0.65, 1.17) to 0.60 (0.22, 1.65). The increased width of the confidence intervals for the RPSFT estimate of the hazard ratio is due to re-censoring of survival events to avoid informative censoring.[101]

The inclusion criteria of the Checkmate-025 trial mandated that patients must have received one or two previous regimens of anti-angiogenic therapy to be eligible for randomisation. In order to provide a comparison of nivolumab to axitinib within the most comparable patient population, the HR utilised for the AXIS trial is that derived for the subgroup of patients previously treated with sunitinib.

Table 17: Summary of trial results contributing to network meta-analysis OS

Trial name	Test	Control	ITT HR [95% CI][a] (OS)	Crossover adjusted/free HR [95% CI] (OS)
CheckMate 025	Nivolumab	Everolimus	0.73 [0.57, 0.93][b]	NA
AXIS[68]	Axitinib	Sorafenib	1.00 [0.78, 1.27][c]	NA
GOLD[75]	Dovitinib	Sorafenib	0.96 [0.75, 1.22]	NA
INTORSECT[77]	Temsirolimus	Sorafenib	1.31 [1.05, 1.63]	NA
RECORD-1[51]	Everolimus	Placebo	0.87 [0.65,1.17]	0.60 [0.22,1.65][d100]
TARGET[85]	Sorafenib	Placebo	0.88 [0.74, 1.04]	0.72 [0.54, 0.94][e85]
VEG105192[87]	Pazopanib	Placebo	0.82 [0.57, 1.16]	0.53 [0.32,1.11][d87]
Yang et al. 2003[89]	Placebo	Bevacizumab[f]	1.09 [0.62, 1.57]	NA

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.
Notes: [a], data presented to two decimal places; [b], 98.5% has been reported in line with the results of the primary analysis; [c], prior sunitinib subgroup data; [d], IPCW estimate; [e], crossover free estimate; [f], doses of 3 mg and 10 mg q2w have been combined. Hazard ratios obtained using digitisation of survival curves.

4.10.5 Evidence base for progression-free survival

Figure 17 presents the treatment network for PFS. Table 18 presents the ITT hazard ratio and 95% CI of the trials contributing to the network meta-analysis of PFS. The network is the same as that used for OS with the addition of the TIVO-1 trial: tivozanib versus sorafenib (Table 15).

The definition of PFS was consistent across eight of the nine studies analysed, though it was not reported for one study.[89] When studies reported both PFS assessed by investigator and centrally read assessment, preference was given to centrally assessed PFS. PFS assessments were made by independent review committee in five studies (Gold trial 2014; Intorsect trial 2014; Record-1 trial 2010; Tivo-1 trial 2013; VEG105192 trial 2013), while in three studies PFS was investigator assessed (Axis trial 2011; CheckMate-025 2015; Target trial 2007). For the remaining one study, the type of assessment was unclear.[89]

Table 18: Summary of trial results contributing to network meta-analysis of PFS

Trial name	Test	Control	ITT HR [95% CI]* (PFS)	Independent review or investigator assessed PFS
CheckMate 025	Nivolumab	Everolimus	0.88 [0.75, 1.03]	Investigator assessed
AXIS[68]	Axitinib	Sorafenib	0.74 [0.57, 0.96]	Investigator assessed
GOLD[75]	Dovitinib	Sorafenib	0.86 [0.72, 1.04]	Independent review
INTORSECT[77]	Temsirolimus	Sorafenib	0.87 [0.71, 1.07]	Independent review
RECORD-1[51]	Everolimus	Placebo	0.33 [0.25, 0.43]	Independent review
TARGET[85]	Sorafenib	Placebo	0.51 [0.43, 0.60]	Investigator assessed
VEG105192[87]	Pazopanib	Placebo	0.54 [0.35, 0.84]	Independent review
Yang et al. 2003[89]	Placebo	Bevacizumab**	0.48 [0.34, 0.62]	Unknown
TIVO-1 trial	Tivozanib	Sorafenib	0.88 [0.59, 1.31]	Independent review

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.
Notes:
*Data presented to two decimal places.
**Doses of 3 mg and 10 mg q2w have been combined. Hazard ratios obtained using digitisation of survival curves.

4.10.6 Results

Overall survival

Figure 18 presents network meta-analysis results for OS. Nivolumab has been used as the reference treatment; results have been presented for the ITT analysis and for the crossover adjusted/crossover free analysis. The interpretation of results focuses on the treatments relevant to the decision problem: nivolumab, axitinib, everolimus and placebo (as a proxy for BSC).

As observed in head-to-head analysis (see Section 4.7), for both the ITT analysis and crossover analysis, nivolumab showed a superior OS benefit with nivolumab

compared to everolimus: HR=0.73 (95% CI: 0.60, 0.89). The point estimate of this comparison remains unaltered from the CheckMate 025 trial (as we may expect *a priori* given this is the only trial of nivolumab compared to everolimus within the network) but the CI width differs (a 98.5% CI width was used for the primary analysis to coincide with the O'Brien–Fleming alpha-spending function used to control the type-1 error rate for the primary analysis of OS, a 95% CI is used in the NMA).

Using the ITT treatment network, nivolumab also shows a numerical advantage against all other treatments (Figure 18a). The HRs [95% CI] for the comparisons of nivolumab to axitinib and placebo are [redacted] and [redacted], respectively.

Using the crossover-adjusted network shows a greater numerical advantage of nivolumab compared to axitinib and placebo than the ITT network; [redacted] and [redacted], respectively. This increased treatment effect of nivolumab compared to axitinib and placebo for the crossover adjusted analysis is predominately driven by the RPSFT result used for the RECORD-1 trial; the point estimate of the survival advantage provided by everolimus compared to placebo is larger using the RPSFT method than the ITT method; RPSFT HR = 0.60 [0.22, 1.65] and ITT HR = 0.87 [0.65, 1.17].

However, the RPSFT result used for the RECORD-1 trial also increases the uncertainty (width of CIs) for these comparisons; the CI derived using the RPSFT method is wider than that of the ITT method, due to re-censoring of survival events (see Section 4.10.4).

The NMA for OS for ITT and for the crossover adjusted/crossover free results using everolimus as a reference treatment are presented in Appendix 7.

Figure 18: Mixed treatment comparison results for overall survival, HRs for nivolumab versus each alternative

[redacted]

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

Progression free survival

Figure 19 presents NMA results for PFS. The results have been presented using nivolumab and everolimus as the reference treatment. The interpretation of results focuses on the treatments relevant to the decision problem; nivolumab, axitinib, everolimus and placebo (as a proxy for BSC).

Again, as observed in head-to-head analysis (see Section 4.7), nivolumab showed a superior PFS benefit compared to everolimus: HR=0.88 (95% CI: 0.75, 1.03) (Figure

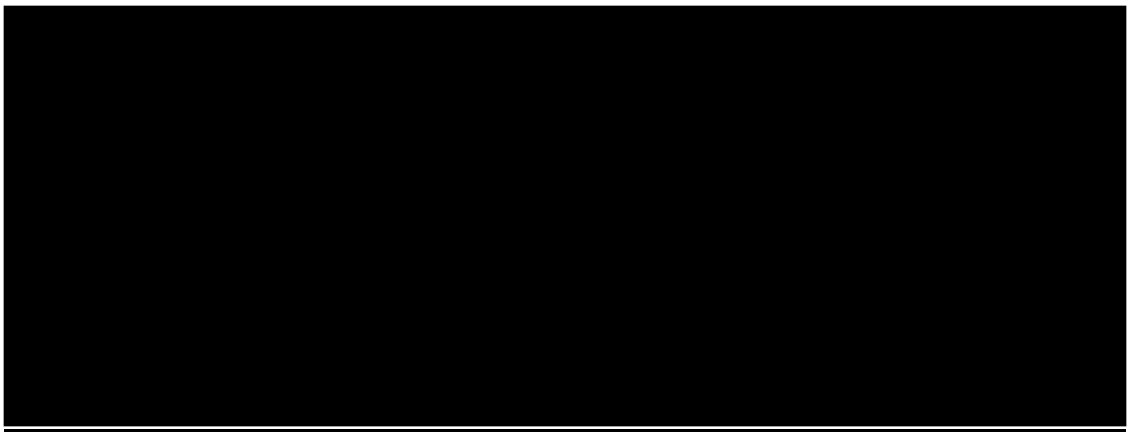
19a) and the point estimate of this comparison remains unaltered from the CheckMate 025 trial. As noted previously, the lack of proportional hazards within CheckMate 025 for the comparison of PFS warrant some caution when interpreting the results.

Using nivolumab as a reference treatment (Figure 19), a superior PFS benefit was also demonstrated compared to axitinib and placebo; [redacted] and [redacted], respectively.

Using everolimus as a reference treatment (Figure 19b), there is superior PFS benefit of everolimus compared to placebo; [redacted]. There is also a numerical advantage of everolimus compared to axitinib; [redacted]. Note, the HR and CI for nivolumab (1.14 [0.97, 1.33]) is the reciprocal of that presented above.

Figure 19: Mixed treatment comparison results for progression free survival, HRs for nivolumab versus each alternative

[redacted]



Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

4.10.7 Conclusion

Nivolumab demonstrated a consistently superior overall survival advantage to all treatments in the network in both the ITT and crossover adjusted analyses. In NHS England, most patients with advanced RCC who have received prior therapy are treated with axitinib (see Section 3.2). Compared to this agent, nivolumab demonstrates a numerically superior OS benefit in both the ITT analysis ( ) and the crossover adjusted analysis ( ). While this benefit was not shown to be significant at the 5% level, the uncertainty for nivolumab versus axitinib can be explained, at least in part, by the position of axitinib in relation to nivolumab in the network. As discussed earlier in this section, the increased treatment effect of nivolumab compared to axitinib and placebo for the crossover adjusted analysis was predominately driven by the RPSFT result used for the RECORD-1 trial, in which the point estimate of the survival advantage provided by everolimus compared to placebo was larger using the RPSFT method than the ITT method (RPSFT HR = 0.60 [0.22, 1.64] and ITT HR = 0.87 [0.65, 1.17]). The increase in uncertainty in the RPSFT result is due to the re-censoring of survival events to avoid informative censoring.[101]

To evaluate the long-term cost effectiveness of nivolumab versus all relevant comparators specified in the scope of the decision problem, results from the crossover-adjusted NMA will be utilised. The crossover adjusted NMA is considered a better reflection of the survival outcomes expected in English clinical practice. This is further supported by the NICE appraisal for everolimus[62], in which the clinical

effectiveness of everolimus was derived using only the RECORD-1 trial. The committee concluded that it was appropriate to evaluate the cost effectiveness of everolimus based on survival estimates generated using the RPSFT crossover adjustment method.

Nivolumab also demonstrated a consistently superior PFS advantage to all treatments in the network, including axitinib ([redacted]). This is despite the fact that PFS analysis within the CheckMate 025 trial is likely to be a conservative estimate of the PFS advantage that may be observed in clinical practice as it does not allow for consideration of the tumour flare phenomenon as a result of the immunotherapy mechanism of action of nivolumab (see Section 4.7).

In light of both nivolumab's different mechanism of action compared to existing RCC treatments and the non-proportional hazards observed for PFS in CheckMate 025, using everolimus as the reference case treatment for the NMA permits flexibility to evaluate the long-term cost-effectiveness of nivolumab versus all relevant comparators specified in the scope of the decision problem. Indeed, assuming proportional hazards across everolimus, axitinib and BSC has merit over the alternative of assuming proportional hazards across nivolumab, axitinib and BSC in consideration of these agents' mechanisms of action and the trial data.

On consultation, some UK RCC-treating oncologists did question the face validity of a suggested benefit for everolimus compared with axitinib, noting that they would have expected survival curves for axitinib to lay above or at least in line with that for everolimus.[102] This expectation is primarily based on response to treatment and delayed disease progression in clinical practice. Indeed, axitinib is associated with greater ORR and PFS results compared with everolimus in their respective pivotal studies when crudely comparing across trials; however, recent research reporting a weight-adjusted indirect comparison of the relative efficacy of everolimus and axitinib[103], using RECORD-1[70] and AXIS data[68], suggest no difference in PFS projections across the two treatments and neither agent has demonstrated a proven OS advantage over the other.

The network meta-analysis presented has been conducted using a relative measure of treatment efficacy; the log hazard ratio. This has been chosen to avoid the requirement for patients recruited to different trials within the network to have, on

average, the same prognosis. This means that the magnitude of treatment effects observed are assumed to be constant across the patient populations recruited to the trials within the network, but it does however allow for differences in absolute values observed. This is important in the case of this evidence base as advancements in subsequent therapies markedly impact the median survival times observed across common treatment arms. For example, the median OS for the everolimus group in CheckMate 025 was 19.6 months compared with a median OS of 14.8 months associated with everolimus in the RECORD-1 trial.

The studies are considered comparable at the level required for NMA. As identified earlier in this section, there are differences between the trials which mean that caution should be applied when interpreting these analyses. Key differences between patient populations include differences in baseline prognostic risk group and prior treatment history; however, within CheckMate 025, subgroup analysis demonstrated that these characteristics were not predictive of OS benefit with nivolumab (see Section 4.8). In addition, while prior treatment was shown to impact median survival times in subgroup analyses of the AXIS trial, the magnitude of treatment effects were not impacted, providing further support for the use of a relative measure network analysis. There is some concern that subgroup analyses from this trial suggest there is an antiangiogenic therapy acquired resistance with VEGFR TKI- VEGFR TKI sequencing which has not been accounted for within this analysis. However, a paucity of evidence prohibits a thorough investigation into this, and without an assumption of comparability despite type of prior treatment, a network for analysis cannot be produced.

The comparison of nivolumab to axitinib (for OS and PFS) is made via three other treatments in the network. There is a paucity of OS RCT data in advanced RCC and for the data available there are high levels of crossover which confound interpretation of mature OS datasets. While this is the best comparison that can be made with the evidence available, the limitations of the analysis should be noted.

4.11 Non-randomised and non-controlled evidence

An additional two clinical trials are considered relevant to the decision problem as they supplement the RCT data presented to support the use of nivolumab in advanced RCC, these trials are summarised in Table 19.

Table 19: List of relevant non-randomised and non-controlled evidence

Trial name (NCT number)	Objective	Population	Intervention	Primary study reference	Justification for inclusion
CheckMate 010 (NCT01354431)	To evaluate whether a dose-response relationship exists for nivolumab	Adult patients with advanced RCC with a clear-cell component who had received prior treatment with at least one anti-angiogenic therapy	Nivolumab 0.3, 2 or 10mg/kg IV Q3W	Motzer et al. 2015[104]	Provides supportive, longer-term data for nivolumab
CheckMate 003 (NCT0730639)	To evaluate the safety, antitumor activity and pharmaco-kinetics of nivolumab	Adult patients with treatment-refractory solid tumours including advanced RCC patients	Nivolumab 1, 3 or 10mg/kg IV Q2W	McDermott et al. 2015[105]	Provides supportive, longer-term data for nivolumab

Key: IV, intravenous; PFS, progression free survival; Q2W, every two weeks; Q3W, every three weeks; RCC, renal cell carcinoma.

Of note, as only non-RCT evidence for nivolumab is considered relevant to the decision problem (as RCT data are available for all comparators to inform the assessment of comparative efficacy and cost-effectiveness in the economic modelling) and nivolumab for advanced RCC is not available outside of BMS sponsored clinical trial programmes, it was not thought necessary to conduct a full systematic review to identify non-RCT evidence presented.

CheckMate 010

Summary of methodology and statistical analysis

CheckMate 010 is a Phase II, dose-ranging trial of nivolumab in patients with clear-cell advanced RCC after prior antiangiogenic therapy.[104] The primary study objective was to evaluate dose-response relationship with nivolumab, as measured by PFS (defined as time from random assignment to date of RECIST-defined progression or death). Secondary study objectives included assessment of OS, ORR and safety.

Patients were randomly assigned to receive 0.3, 2 or 10mg/kg nivolumab administered intravenously every three weeks until disease progression or unacceptable toxicity. As was the case in CheckMate 025, patients could continue treatment post RECIST-assessed progression if there was an investigator-assessed clinical benefit and patients were tolerating treatment. Tumour assessments were performed every 6 weeks for the first 12 months and every 12 weeks thereafter; assessments for survival were performed continuously during treatment and every 3 months during follow-up. The efficacy population included all randomly assigned patients, and the safety population included all patients who received at least one dose of nivolumab.

Sample size calculation resulted in a planned accrual of at least 150 patients to provide a ≥90% power to detect a dose-response relationship across the three treatment arms. Evaluation of a dose-response relationship as measured by PFS was performed using a two-sided 20%-level log-rank trend test stratified by MSKCC risk group and number of prior treatment regimens in the metastatic setting. The HRs and two-sided 80% CIs of the nivolumab 0.3, 2, and 10 mg/kg doses relative to each other dose were estimated using the Cox proportional hazards model, stratified by MSKCC risk group and number of prior therapies, with randomised treatment arm as the single covariate. For each treatment group, ORR was estimated along with an exact 80% CI using the Clopper-Pearson method. The dose-response relationship was evaluated using a two-sided 20%-level Cochran-Armitage test. Median OS and 80% CI for each treatment group were estimated using KM methodology. Data presented are from the primary cut-off of 15 May 2013 for PFS and ORR analyses and from an updated data cut-off of 5 April 2015 for OS analysis, providing a minimum follow-up of 38 months for all patients.[106]

Quality assessment of CheckMate 010, conducted by assessing risk of common types of bias as well as the applicability of study results to the decision problem is provided in Appendix 4.

Participant flow

Between May 2011 and January 2012, 168 patients from 39 centres in Northern America and Europe were randomly assigned to one of the treatment arms (0.3mg/kg; n=60; 2mg/kg; n=54; 10mg/kg; n=54).[104] Baseline characteristics were balanced among treatment groups. In total, 70% of patients had received more than one prior systemic regimen for metastatic RCC and 25% of patients met MSKCC poor-risk criteria. Of patients with quantifiable PD-L1 expression at baseline (n=107), 73% had <5% expression.

Patient disposition for CheckMate 010 is presented in Table 20 and baseline demographics and disease characteristics of patients enrolled are presented in Table 21.

Table 20: Patient disposition in CheckMate 010

	Nivolumab 0.3mg/kg (n=60)	Nivolumab 2mg/kg (n=54)	Nivolumab 10mg/kg (n=54)
Patients who received treatment, n (%)	59 (98)	54 (100)	54 (100)
Discontinuations, n (%)	53 (90)	52 (96)	50 (93)
Discontinuation due to disease progression, n (%)	49 (83)	40 (74)	41 (76)
Discontinuation due to TRAE, n (%)	2 (3)	7 (13)	4 (7)
Key: TRAE, treatment-related adverse event. **Source**: Plimack et al. 2015.[106]			

Table 21: Characteristics of patients in CheckMate 010

Baseline characteristic	Nivolumab 0.3 mg/kg (n=60)	Nivolumab 2 mg/kg (n=54)	Nivolumab 10 mg/kg (n=54)
Age, median years (range)	61 (9)	61 (8)	61 (10)
Gender, male n (%)	41 (68)	40 (74)	40 (74)
MSKCC risk group, n (%) Favourable Intermediate Poor	 20 (33) 26 (43) : 14 (23)	 18 (33) 22 (41) : 14 (26)	 18 (33) 22 (41) 14 (26)
Karnofsky PS, n (%) 70 or 80 90 or 100	 22 (37) 38 (63)	 30 (56) 24 (44)	 25 (46) 28 (52)
Common metastasis site, n (%)	Lung: 46 (77) Lymph node: 29 (48) Liver: 15 (25) Skin/soft tissue: 18 (30) Adrenal: 8 (13)	Lung: 39 (72) Lymph node: 35 (65) Liver: 13 (24) Skin/soft tissue: 11 (20) Adrenal: 19 (35)	Lung: 39 (72) Lymph node: 34 (63) Liver: 19 (35) Skin/soft tissue: 11 (20) Adrenal: 10 (19)
Previous antiangiogenic regimens, n (%)	1: 34 (57) 2: 22 (37) 3: 4 (7)	1: 35 (65) 2: 16 (30) 3: 3 (6)	1: 35 (65) 2: 18 (33) 3: 1 (2)
Previous systemic therapy, n (%)	Sunitinib: 46 (7) Everolimus: 21 (35) Pazopanib: 15 (25) IL-2: 15 (25) Sorafenib: 13 (22)	Sunitinib: 42 (78) Everolimus: 18 (33) Pazopanib: 18 (33) IL-2: 11 (20) Sorafenib: 8 (15)	Sunitinib: 37 (69) Everolimus: 18 (33) Pazopanib: 13 (24) IL-2: 12 (22) Sorafenib: 19 (31)
Key: MSKCC, Memorial Sloan-Kettering Cancer Centre; PD-L1, programmed death receptor ligand 1; PS, performance status; SD, standard deviation. **Source**: Motzer et al. 2015.[104]			

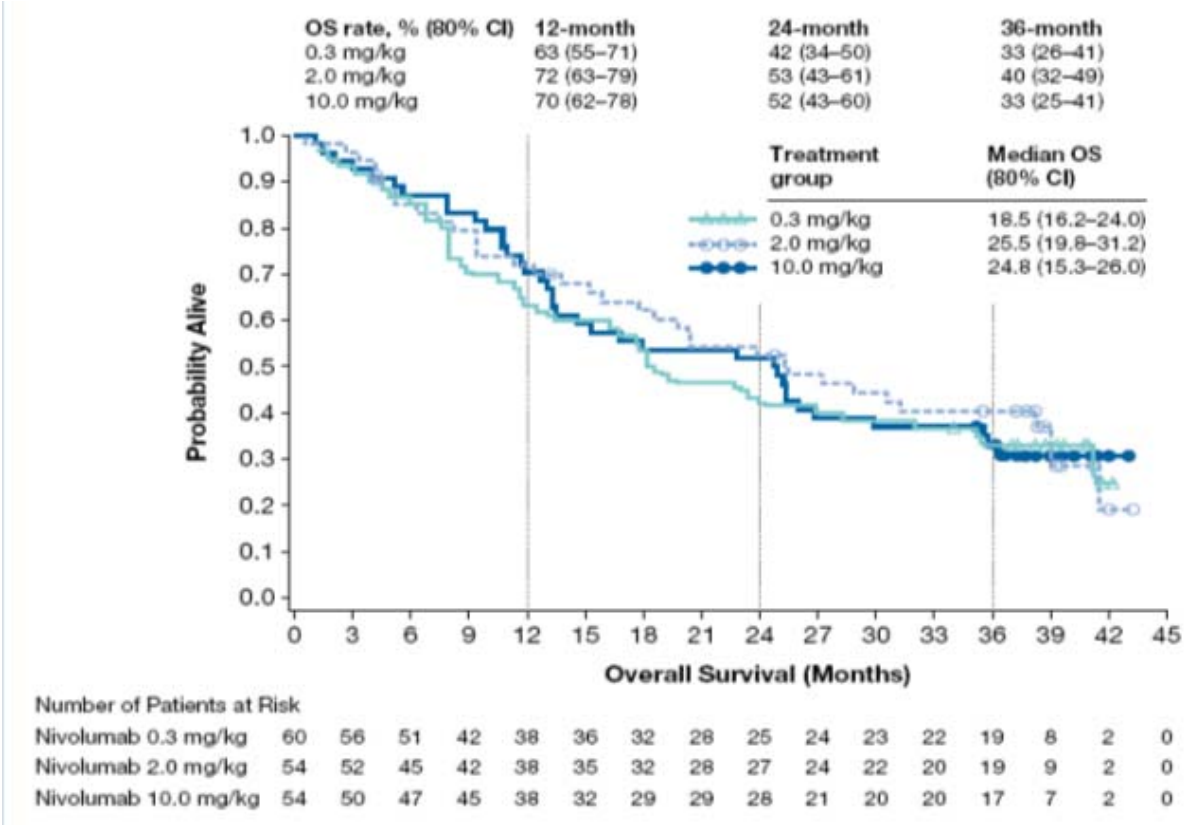
Clinical effectiveness

In primary outcome analysis, median PFS was 2.7 months (80% CI: 1.9 to 3.0 months), 4.0 months (80% CI: 2.8 to 4.2 months) and 4.2 months (80% CI: 2.8 to 5.5 months) for the 0.3, 2 and 10 mg/kg nivolumab groups, respectively and no dose-response relationship for PFS was detected (p=0.9). [104, 106]

In follow-up analysis, median OS was 18.5 months (80% CI: 16.2 to 24.0 months), 25.5 months (80% CI: 19.8 to 31.2 months), and 24.8 months (80% CI: 15.3 to 26.0 months) in the 0.3, 2, and 10 mg/kg groups, respectively, and 3-year OS rates were 33-40% depending on nivolumab dose.[106]. OS analyses were again consistent across subgroups including those associated with poorer prognosis and PD-L1 expression status at baseline.

The KM curve for OS is presented in Figure 20.

Figure 20: Kaplan-Meier plot for OS in CheckMate 010, all randomised patients



Key: CI, confidence interval; OS, overall survival.
Source: Plimack et al. 2015.[106]

Nivolumab therapy resulted in consistent ORR regardless of dose: 20% (n=12), 22% (n=12), and 20% (n=11) in the 0.3, 2, and 10 mg/kg groups, respectively. Median duration of response (DOR) was not reached in either the 0.3 or 2 mg/kg groups but was 22.3 months 80% (CI: 4.8 months to not reached) in the 10 mg/kg group; 40% of patients were still responding to nivolumab treatment 2-years post treatment initiation.

CheckMate 003

Summary of methodology and statistical analysis

CheckMate 003 is a Phase 1b, open-label, dose-escalation trial of nivolumab in patients with selected advanced or recurrent malignancies, including RCC, who had received up to five prior systemic therapies.[105] The primary study objective was to assess the safety and tolerability of nivolumab, and on the basis of observed objective responses, the protocol was amended to include OS as an exploratory endpoint.

During the dose-escalation phase, patients received nivolumab 1, 3 or 10mg/kg intravenously every 2 weeks in 8 week treatment cycles. The RCC population was treated with nivolumab 10mg/kg in an initial expansion cohort, followed by a subsequent expansion cohort at 1 mg/kg. Treatment continued up to 96 weeks (12 cycles), or until patients experienced confirmed complete response, disease progression or unacceptable toxicity. Again, patients could continue treatment post RECIST-assessed progression if there was an investigator-assessed clinical benefit and patients were tolerating treatment. Tumour assessments were performed after each 8 week treatment cycle against RECIST; assessments for survival were performed continuously during treatment and every 3 months during follow-up. Patients with stable disease or ongoing response at the end of treatment were observed for up to 1 year and offered retreatment for 1 additional year if disease progressed. The efficacy population included all randomly assigned patients, and the safety population included all patients who received at least one dose of nivolumab.

Objective response and stable disease rates were estimated with CIs using the Clopper-Pearson method. Time-to-event end points, including PFS, OS, survival rates and response duration were estimated using the KM method with CIs for the medians based on the Brookmeyer-Crowley method and CIs for overall and progression-free survival rates based on the Greenwood formula. Efficacy analyses are reported as of September 2013 when the median follow-up was 45.2 months; baseline characteristics are reported as of March 2013.

Quality assessment of CheckMate 003, conducted by assessing risk of common types of bias as well as the applicability of study results to the decision problem, is provided in Appendix 4.

Participant flow

Between November 2008 to January 2012, 34 patients with pre-treated advanced RCC began treatment with nivolumab (1mg/kg; n=18; 10mg/kg; n=16). Baseline characteristics of these patients are presented in Table 22.

Table 22: Characteristics of advanced RCC patients in CheckMate 003

Baseline characteristic	Nivolumab (n=34)
Age, median years (range)	58 (35-74)
Gender, male n (%)	26 (76)
ECOG PS, n (%)	0: 17 (50) 1: 17 (50)
Common metastasis site, n (%)	Bone: 10 (29) Liver: 9 (27) Lung: 30 (88) Lymph node: 28 (82) Any visceral site: 30 (88)
Prior antiangiogenic treatment, n (%)	24 (71)
Previous systemic regimens, n (%)	1: 10 (29) 2: 9 (27) 3: 6 (18) ≥4: 9 (27)
Previous systemic therapy, n (%)	Hormonal, immunologic, or biologic: 24 (71) Chemotherapy: 19 (56) mTOR inhibitor: 11 (32) Radiotherapy: 10 (29)
Key: ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; PS, performance status; RCC, renal cell carcinoma. **Source**: McDermott et al. 2015.[105]	

Clinical effectiveness

Median OS was 22.4 months in RCC patients receiving nivolumab at 1 or 10 mg/kg and 1-year, 2-year and 3-year survival rates were 71%, 48%, and 44%, respectively.[105] Median PFS was 7.3 months, with 1- and 2-year PFS rates of 35% and 12%, respectively.

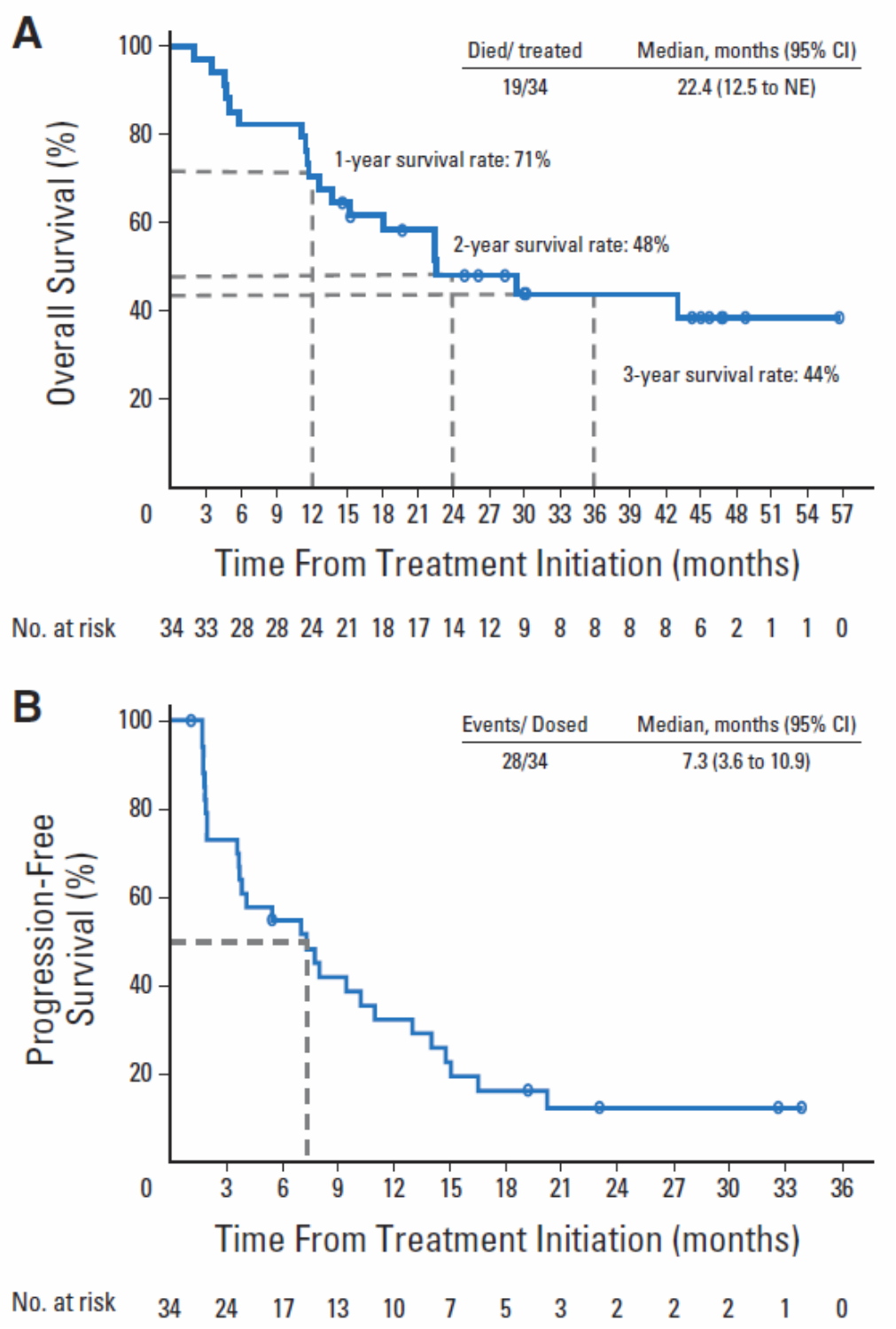
The KM curves for OS and PFS are presented in Figure 21.

In response analyses, objective response was observed in 29% (10/34) of RCC patients treated at either nivolumab dose (1 or 10mg/kg); an additional 27% of

patients (9/34) experienced stable disease lasting for at least 24 weeks. In the 10 patients with a complete or partial response to nivolumab treatment, the median DOR was 12.9 months (range: 8.4 to 29.1+ months). Four (40%) of 10 responses were ongoing at the time of data analysis, including three that persisted for approximately one year after treatment discontinuation.

More recent OS data with a median follow-up of 50.5 months have recently become available and are due to be reported at ASCO 2016. These data report a 5-year survival rate of 34% associated with nivolumab therapy.

Figure 21: Kaplan-Meier plot of OS (A) and PFS (B) in CheckMate 003, advanced RCC patients



Key: CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.
Source: McDermott et al. 2015.[105]

4.12 Adverse reactions

Apart from the studies presented in Section 4.2 and 4.11, no other studies investigate nivolumab within the indication being appraised; safety data are therefore only presented from CheckMate 025, CheckMate 010 and CheckMate 003.

CheckMate 025

Treatment exposure

In this study, 406 patients received at least one infusion of nivolumab 3mg/kg and 397 patients received at least one dose of 10mg everolimus as an oral dose.[71, 90] The majority of patients ([redacted]) in the nivolumab group and [redacted] of patients in the everolimus group received ≥90% of the planned dose intensity. In the nivolumab group, the median number of doses received was [redacted] (range: [redacted] to [redacted]) and in the everolimus group, the median daily dose was [redacted] mg/day.

The median duration of nivolumab treatment was 5.5 months (range: <0.1 to 29.6) with [redacted] of patients having discontinued treatment by 20 months. The median duration of everolimus treatment was 3.7 months (range: 0.2 to 25.7).

The KM plot for duration of study therapy is presented in Figure 22.

In total, 207 of the 406 patients treated with nivolumab (51%) had dose delays, and 262 of the 397 patients treated with everolimus (66%) had dose delays (including interruptions). A total of 102 of the 397 patients in the everolimus group (26%) had at least one dose reduction; dose reductions were not allowed with nivolumab.

Figure 22: [redacted]

Key: CI, confidence interval; CSR, clinical study report.
Source: CheckMate 025 CSR.[71]

Safety profile

The majority of patients in both treatment groups of CheckMate 025 experienced at least one AE of any grade.[71, 90] However, there was a lower rate of treatment-related AEs (TRAEs) (all grades and Grades 3-4) in the nivolumab group compared to the everolimus group, as well as a lower frequency of TRAEs leading to discontinuation (all grades and Grades 3-4). Importantly, there were no treatment-related deaths in the nivolumab group compared to 2 in the everolimus group (one from septic shock and one from acute bowel ischemia).

Summary safety data are presented in Table 23.

Table 23: Summary of safety data from CheckMate 025, all treated patients

	Nivolumab (n=406)	Everolimus (n=397)
All AEs, n (%)	[redacted]	[redacted]
Grade 3-4 AEs, n (%)	[redacted]	[redacted]
TRAEs, n (%)	319 (78.6)	349 (87.9)
Grade 3-4 TRAEs, n (%)	76 (19)	145 (37)
All SAEs, n (%)	[redacted]	[redacted]
TRSAEs, n (%)	[redacted]	[redacted]
DC due to AEs, n (%)	[redacted]	[redacted]
DC due to TRAEs, n (%)	31 (7.6)	52 (13.1)
DC due to Grade 3-4 TRAEs, n (%)	[redacted]	[redacted]
Deaths relating to study drug, n (%)	0	2 (0.5)

Key: AE, adverse event; DC, discontinuation; SAE, serious adverse event; TRAE, treatment related adverse event; TRSAE, treatment related serious adverse event
Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]

All-causality adverse events

The most frequently reported AEs in the nivolumab group were: fatigue ([redacted]); cough ([redacted]); nausea ([redacted]); diarrhoea ([redacted]); dyspnoea ([redacted]); constipation ([redacted]); decreased appetite ([redacted]) and back pain ([redacted]).[90] For the everolimus group, AEs reported in ≥20% of patients included: fatigue ([redacted]), cough ([redacted]), anaemia ([redacted]), stomatitis ([redacted]), diarrhoea ([redacted]), decreased appetite ([redacted]), nausea ([redacted]), dyspnoea ([redacted]), peripheral oedema ([redacted]), rash ([redacted]), mucosal inflammation ([redacted]), and pyrexia ([redacted]).

Common Grade 3-4 AEs were similar in nature, those reported in more patients treated with nivolumab versus everolimus were hypercalcaemia ([redacted] vs [redacted]), increased alanine aminotransferase ([redacted]versus[redacted]) and malignant neoplasm progression ([redacted] versus [redacted]). Grade 3-4 AEs reported in more patients treated with everolimus versus nivolumab were anaemia ([redacted] versus [redacted]), hyperglycaemia ([redacted] versus [redacted]), hypertriglyceridemia ([redacted] versus [redacted]), stomatitis ([redacted] versus [redacted]), and mucosal inflammation ([redacted] versus [redacted]).

Treatment-related adverse events

The most common TRAEs among patients who received nivolumab were fatigue, nausea and pruritus; among patients who received everolimus, the most common events were fatigue, stomatitis, and anaemia.[71, 90] In the nivolumab group, the only Grade 3-4 TRAE reported by more than 2% of patients was fatigue, reported in 10 patients (3%). In comparison, Grade 3-4 TRAEs of anaemia, hypertriglyceridemia, stomatitis, hyperglycaemia, mucosal inflammation, pneumonitis and fatigue were all reported by more than 2% of patients treated with everolimus.

A summary of TRAEs of all grades is presented in Table 24.

Table 24: Summary of TRAEs (≥10%) by worst CTC grade (any grade, Grade 3-4, Grade 5), all treated patients

	Nivolumab (n=406)			Everolimus (n=397)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
All TRAEs, n (%)	319 (78.6)	76 (18.7)	0	349 (87.9)	145 (36.5)	2 (0.5)
Fatigue	134 (33.0)	10 (2.5)	0	134 (33.8)	11 (2.8)	0
Stomatitis	8 (2.0)	0	0	117 (29.5)	17 (4.3)	0
Anaemia	32 (7.9)	7 (1.7)	0	94 (23.7)	31 (7.8)	0
Diarrhoea	50 (12.3)	5 (1.2)	0	84 (21.2)	5 (1.3)	0
Decreased appetite	48 (11.8)	2 (0.5)	0	82 (20.7)	4 (1.0)	0
Rash	41 (10.1)	2 (0.5)	0	79 (19.9)	3 (0.8)	0
Cough	36 (8.9)	0	0	77 (19.4)	0	0
Mucosal inflammation	11 (2.7)	0	0	75 (18.9)	12 (3.0)	0
Nausea	57 (14.0)	1 (0.2)	0	66 (16.6)	3 (0.8)	0
Hypertriglyceridemia	5 (1.2)	0	0	64 (16.1)	20 (5.0)	0
Pneumonitis	16 (3.9)	6 (1.5)	0	58 (14.6)	11 (2.8)	0
Oedema peripheral	17 (4.2)	0	0	56 (14.1)	2 (0.5)	0
Pruritus	57 (14.0)	0	0	39 (9.8)	0	0
Dyspnoea	30 (7.4)	3 (0.7)	0	51 (12.8)	2 (0.5)	0
Hyperglycaemia	9 (2.2)	5 (1.2)	0	46 (11.6)	15 (3.8)	0
Epistaxis	3 (0.7)	0	0	41 (10.3)	0	0

Key: CTC, common terminology criteria; TRAEs, treatment related adverse events.
Source: CheckMate 025 CSR[71]; Motzer et al. 2015.[90]

Serious adverse events

The overall frequency of serious adverse events (SAEs) and treatment-related serious adverse events (TRSAEs) were similar between the treatment groups (Table 23).[71, 90] The most frequently reported SAEs were also similar between the treatment groups with the only non-common SAE reported by more than 2% of patients being anaemia, reported in [redacted] of patients treated with everolimus compared with [redacted] of patients treated with nivolumab. The most frequently reported TRSAEs in the nivolumab group were pneumonitis ([redacted]) and diarrhoea ([redacted]); the most frequently reported TRSAEs in the everolimus group were pneumonitis ([redacted]), anaemia ([redacted]) and pneumonia ([redacted]).

Select adverse events

Select AEs, defined as AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab, were analysed according to organ category (skin, gastrointestinal [GI], endocrine, pulmonary, hepatic, and renal) as in previous studies of immunotherapies.

Among nivolumab treated patients, skin, GI, renal and hepatic were the most frequently reported Select AE categories ([redacted] of patients regardless of causality).[71] Among everolimus treated patients, GI, pulmonary and skin were the most frequently reported Select AE categories. Between groups, more patients treated with nivolumab reported Select AEs belonging to the endocrine, hepatic and hypersensitivity/infusion reaction categories while more patients treated with everolimus reported Select AEs belonging to the GI, pulmonary and skin categories.

The median time to onset of Select AEs varied among categories, but did not exceed [redacted] months ([redacted] weeks) in any category, demonstrating the rarity of delayed side-effects of nivolumab treatment. Across Select AE categories, the majority of events were transient and readily manageable with dose interruptions or administration of immune-modulating medications (mostly systemic corticosteroids) in line with established safety algorithms. Resolution rates were lowest in the endocrine category due to the continuing need for hormone replacement therapy.

A summary of Select AE data is presented in Table 25.

Table 25: Summary of Select AEs reported up to 30 days after last dose, all treated patients

	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	**Treatment-related**	**All causality**	**Treatment-related**
Endocrine	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]

	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	**Treatment-related**	**All causality**	**Treatment-related**
Gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Renal	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/	[redacted]	[redacted]	[redacted]	[redacted]

	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	**Treatment-related**	**All causality**	**Treatment-related**
Infusion reactions				
Grade 3-4	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution, median weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CSR, clinical study report.
Source: CheckMate 025 CSR.[71]

CheckMate 010 and CheckMate 003

Similar safety profiles were observed with nivolumab regardless of dose in supportive trials and were similar to that observed in CheckMate 025, that is, most patients experienced a TRAE, but the nature of events was consistent with the mechanism of action of nivolumab and therefore anticipated *a priori*.

In both CheckMate 010 and CheckMate 003 (as was the case in CheckMate 025) the most commonly reported TRAE was fatigue, reported in 24%, 22% and 35% of patients treated with nivolumab at doses of 0.3, 2 and 10mg/kg, respectively in CheckMate 010 and in 41% of advanced RCC patients treated with nivolumab (regardless of dose) in CheckMate 003. [104, 105]

Discontinuations due to TRAEs were low (<10%) in both trials and, importantly, there were no deaths due to study-drug toxicity reported in either CheckMate 010 or in the advanced RCC group of patients enrolled in CheckMate 003.

Comparator safety

Qualitative synthesis of common AEs suggests a similar safety advantage for nivolumab versus axitinib as was observed versus everolimus in the CheckMate 025 trial, as summarised in Table 26.

TRAEs of diarrhoea, hypertension, decreased appetite, nausea, dysphonia, hand-foot syndrome, hypothyroidism, weight decrease, asthenia, vomiting, mucosal inflammation, stomatitis and proteinuria were all more common with axitinib than with

nivolumab (greater than 10% difference between treatment groups). [50, 90] As noted previously, the only Grade 3-4 TRAE reported by more than 2% of patients treated with nivolumab in CheckMate 025 was fatigue.

In the AXIS trial, Grade 3-4 TRAEs of hypertension, diarrhoea, hand-foot syndrome, decreased appetite, asthenia, weight decrease and proteinuria were reported by more than 2% of patients treated with axitinib in addition to fatigue.

Table 26: Summary of TRAEs (≥10%) from the axitinib arm of AXIS and the nivolumab arm of CheckMate 025[a]

	Axitinib (n=359)		Nivolumab (n=406)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhoea	193 (53.8)	40 (11.1)	50 (12.3)	5 (1.2)
Hypertension	149 (41.5)	60 (16.7)	6 (1.5)	3 (0.7)
Fatigue	133 (37.0)	37 (10.3)	134 (33.0)	10 (2.5)
Decreased appetite	113 (31.5)	15 (4.2)	48 (11.8)	2 (0.5)
Nausea	109 (30.4)	6 (1.7)	57 (14.0)	1 (0.2)
Dysphonia	102 (28.4)	0	7 (1.7)	0
Hand-foot syndrome	100 (27.9)	20 (5.6)	-	-
Hypothyroidism	72 (20.1)	1 (<0.5)	24 (5.9)	1 (0.2)
Weight decreased	70 (19.5)	12 (3.3)	19 (4.7)	1 (0.2)
Asthenia	66 (18.4)	15 (4.2)	18 (4.4)	1 (0.2)
Vomiting	63 (17.5)	5 (1.4)	24 (5.9)	0
Mucosal inflammation	58 (16.2)	5 (1.4)	11 (2.7)	0
Stomatitis	55 (15.3)	5 (1.4)	8 (2.0)	0
Rash	47 (13.1)	1 (<0.5)	41 (10.1)	2 (0.5)
Constipation	45 (12.5)	1 (<0.5)	24 (5.9)	1 (0.2)
Proteinuria	45 (12.5)	11 (3.1)	1 (0.2)	0
Dysgeusia	41 (11.4)	0	11 (2.7)	0
Headache	39 (10.9)	3 (0.8)	24 (5.9)	0
Arthralgia	36 (10.0)	3 (0.8)	27 (6.7)	1 (0.2)
Dry skin	36 (10.0)	0	26 (6.4)	0
Pruritus	22 (6.1)	0	57 (14.0)	1 (0.2)

Notes: [a], this is not intended as a cross-trial comparison because of drawbacks of differences in trial design.
Source: CheckMate 025 CSR[71]; Motzer et al. 2013 [50]; Motzer et al. 2015.[90]

Dose reductions were reported in 34% (121/359) of axitinib-treated patients in the AXIS trial, while being mindful of cross-trial comparisons, we note that this is higher than the dose reduction rate of everolimus-treated patients in the CheckMate 025 trial (26%).This supports the opinion of the UK RCC-treating oncologists, consulted during preparation of this submission, who feel that additional toxicity is observed with VEGFR TKI's compared with mTOR inhibitor therapy in clinical practice.[102]

4.13 Interpretation of clinical effectiveness and safety evidence

Advanced RCC is an immunogenic disease with an overall poor prognosis. Despite significant therapeutic advancements over the last decade, there are only a few active treatment options available for patients with advanced RCC who have received prior therapy, resulting in sequencing of the same drug class commonly observed in the management approach. Active treatments that are available do not offer a proven OS benefit and are associated with toxicity profiles that may counteract positive benefit from clinical efficacy on the patient's quality of life. As a result, a proportion of patients do not receive active treatment post first-line therapy and are simply managed with BSC.

There is a clear unmet medical need for a tolerable treatment option with proven survival and quality of life benefit for patients with advanced RCC who have received prior therapy. Nivolumab meets this unmet need.

Principal findings from the clinical evidence base

The clinical benefits and potential harms associated with nivolumab have been comprehensively demonstrated in a high-quality clinical trial programme. Principal findings from the evidence base supporting the use of nivolumab within the indication for which it is being appraised here are summarised below:

<u>Nivolumab offers a proven survival benefit to patients with advanced RCC who have received prior therapy</u>

In the pivotal Phase III trial, CheckMate 025, nivolumab was associated with over a 5 month improvement in OS compared with conventional targeted therapy (everolimus): 25.0 versus 19.6 months; HR for death: 0.73 (98.5% CI, 0.57 to 0.93); p=0.002. The potential for longer-term survival benefit with nivolumab therapy is

supported with Phase I/II trial data that reports 3-year survival rates of 33-44%, depending on nivolumab dose (0.3 to 10mg/kg) and a 5-year survival rate of 34%; this is a marked improvement on the current 5-year survival estimates in advanced RCC of 10-15% (see Section 3.3). Furthermore, nivolumab has demonstrated an immune-response OS tail in melanoma patients (NICE ID845), while such a tail is not observed in the CheckMate 025 trial, this may be due to insufficient follow-up and patients numbers that were not powered to detect such an effect. Indeed, UK oncologists have expressed an expectation of longer-term survival to be observed in clinical practice in line with the immunotherapy mechanism of action.[102]

Survival benefit was observed irrespective of patient characteristics and baseline prognosis, including in pre-specified subgroup analyses based on PD-L1 tumour expression status. With remarkably similar HRs for death across ITT, PD-L1 positive and PD-L1 negative populations (0.73, 0.77 and 0.77, respectively), but differences in absolute median OS times observed (25.0, 21.8 and 27.4 months, respectively), CheckMate 025 adds further support to the current opinion that PD-L1 tumour expression is not a predictive biomarker for nivolumab response, but may be a prognostic biomarker in RCC.

Nivolumab is associated with improved clinical response in patients with advanced RCC who have received prior therapy

Nivolumab therapy resulted in a significant increase in ORR compared with conventional targeted therapy (everolimus) in CheckMate 025: 25% versus 5%; OR: 5.98 (95% CI, 3.68 to 9.72); p<0.001. The majority of clinical responses to nivolumab occurred within the first 4 months of treatment (median time to response of 3.5 months) and 31% of patients demonstrated an ongoing response of at least 12 months duration at the time of analysis. In patients with confirmed objective response (n=104), median duration of response was [redacted] months in the nivolumab group compared with [redacted] months in the everolimus group.

This durability of clinical response with nivolumab in at least a proportion of patients is supported with Phase I/II trial data that reports ongoing responses of at least 2 years in approximately 40% of responders. In CheckMate 003 where treatment was

of fixed duration (up to 96 weeks), 30% of responders had persistent response (approximately 1 year) post treatment discontinuation.

Nivolumab may have a positive impact on the quality of life of patients with advanced RCC who have received prior therapy

Patients treated with nivolumab therapy in CheckMate 025 reported constant improvement in disease-specific HRQL, as indicated by increased scores on the FKSI-DRS questionnaire over time. This improvement was significantly greater than that observed in patients treated with conventional targeted therapy (everolimus) at each assessment point through Week 104 ($p<0.05$).

Over the course of the study, significantly more patients treated with nivolumab experienced meaningful DRS and EQ-5D VAS improvement compared with patients treated with everolimus.

Nivolumab demonstrates a favourable safety profile compared with conventional targeted therapy

Common AEs associated with nivolumab therapy are reflective of its therapeutic class and will be familiar to clinicians using immunotherapy drugs in other indications, for example, ipilimumab or PD-1 checkpoint inhibitor therapy in advanced melanoma. Select AEs that do occur are predictable and medically manageable with established safety algorithms (developed to accommodate the safe use of immunotherapy treatments) in the majority.

In CheckMate 025, reduced rates of TRAEs (79% versus 88%), TRAEs of Grade 3-4 (19% versus 37%), dose delays (51% versus 66%), and discontinuations due to TRAEs (8% versus 13%) clearly demonstrate the improved safety profile of nivolumab, compared with everolimus. Importantly, no deaths related to study-drug toxicity were reported across trials of nivolumab in advanced RCC, but two patients treated with everolimus in CheckMate 025 died due to treatment-related complications.

Strengths and limitations of the clinical evidence base

Overall, the clinical evidence available provides an appropriate base to inform the assessment of clinical effectiveness and cost effectiveness of nivolumab for the

treatment of patients with advanced RCC who have received prior therapy in clinical practice.

CheckMate 025 is the first Phase III trial in the advanced RCC arena primarily designed to assess OS in patients who have received prior therapy

Pivotal trials supporting the use of conventional targeted therapy for the treatment of advanced RCC have historically been designed to assess PFS as the primary endpoint. As advanced RCC is not curable, in the first-line setting, PFS may be considered an appropriate endpoint with a primary aim of therapy to delay disease progression and extend time to next treatment. Indeed, the EMA state that PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with effect on OS may importantly hamper the detection of a relevant treatment effect on OS.[107]

However, this does not negate the fact that OS is considered to be the most reliable endpoint in late-stage oncology trials (given its precise and easy to measure, unambiguous nature) and should be the preferred primary endpoint when studies can be conducted to adequately assess survival, such as in the subsequent-line setting where there are few further lines of effective treatment options.[107] Moreover, improved life-expectancy (demonstrated by improved OS) is of primary interest to patients with advanced RCC, particularly those who have progressed on or after first-line therapy.

None of the current treatment options for patients with advanced RCC who have received prior therapy have demonstrated an OS benefit in a Phase III setting.

Trials are well designed with clinically relevant study endpoints

All CheckMate trials are being conducted in line with GCP guidelines, with steps taken to minimise bias and independent monitoring or advisory committees in place to provide oversight of safety and efficacy considerations, study conduct and risk-benefit ratio.

The clinical trial programme was designed to capture endpoints most relevant to patients, clinicians and healthcare providers alike. They therefore not only include clinical efficacy and safety endpoints consistent with other studies of therapeutic agents in advanced RCC, but also include validated assessments of HRQL to aid

cost-effectiveness modelling (see Section 5.5). Of note, clinical efficacy endpoints did include conventional assessments of progression against RECIST, but it is well accepted that such analysis gives a conservative estimate of immunotherapy benefit due to the potential for tumour flare phenomenon with such therapies; this should be considered when interpreting PFS data.

Trial populations are reflective of patient profiles observed in UK clinical practice

Across trials supporting the use of nivolumab within the indication being appraised, populations are reflective of patients presenting for subsequent-line treatment for advanced RCC in UK clinical practice where anti-angiogenic therapy is established standard of care in the first-line setting. Importantly, consistently superior clinical benefit was observed across all pre-determined subgroups, including those presenting with poor prognosis at baseline and those receiving nivolumab at second- or subsequent-line.

In the pivotal Phase III trial, European sites represented approximately half of all involved (69/146). This included four UK sites across which 26 patients were randomised. Furthermore, clinical experts practising in the field of RCC confirmed that they would be comfortable applying CheckMate 025 trial results to patients presenting in UK clinical practice.[12]

Head-to-head data are available for one of the key comparators relevant to NHS England

CheckMate 025 directly compares nivolumab with everolimus, one of the comparators named in the decision problem. While head-to-head data are not available for comparators outside of everolimus, a NMA has been conducted and demonstrates a superior OS benefit of nivolumab compared with axitinib and BSC. As with all indirect estimates, there is uncertainty associated with these analyses, but the approach taken was designed to minimise this uncertainty, despite a paucity of data available and heterogeneity across trials and all sensitivity analyses support trends observed in the base-case analysis.

On consultation, some UK RCC-treating oncologists did question the face validity of a suggested survival benefit for everolimus compared with axitinib as in their experience VEGFR TKI therapy is associated with superior clinical effectiveness

compared with mTOR inhibitor therapy.[102] This view is primarily based on response to treatment and delayed disease progression in clinical practice. Indeed, axitinib is associated with greater ORR and PFS results compared with everolimus in their respective pivotal studies; however, ORR and PFS benefits have not been shown to translate to a superior OS advantage.[51, 68]

In the NMA presented in this submission, key data points connecting the CheckMate 025 and AXIS trials are from the TARGET and RECORD-1 trials. Across these RCTs, everolimus demonstrated a greater OS benefit over placebo than observed with sorafenib when assessing crossover adjusted/crossover free data; a comparable OS benefit is observed in ITT analysis which is more in line with clinical expectation. Importantly, the survival benefit associated with nivolumab compared with axitinib is constant across ITT and crossover adjusted NMA and oncologists were unanimous in their expectation that nivolumab would result in improved OS compared with both axitinib and everolimus in clinical practice.[102] This opinion is based on trial data as well as biological rationale and clinical experience of immunotherapy agents in other indications; for example, in patients with advanced melanoma, nivolumab recently demonstrated a significant OS advantage over ipilimumab therapy[108] which had previously provided unprecedented OS benefit in this setting.

End of life treatment considerations

The life expectancy of patients with advanced RCC is historically poor with 1-year survival rates reported at approximately 40% (2006-2010 data).[31] Survival rates reflecting current practice are not available but since the introduction of targeted therapies, this life expectancy is thought to have improved. This is despite a lack of significant OS benefit being demonstrated for any targeted therapy in a Phase III trial setting and is based on assumptions of longer-term benefit associated with improved response to treatment and delayed disease progression. The contribution of specific agents or specific treatment sequences to improvements in OS remains unclear but active treatment options of axitinib and everolimus are associated with median OS estimates of approximately 20 months in clinical trials. For patients who progress after first-line therapy and do not have a second-line treatment option, median OS estimates are still <12 months.

Head-to-head trial data demonstrate an extension to life of over 5 months with nivolumab treatment compared with everolimus (HR for death: 0.73). Superior OS benefit is estimated in NMA of nivolumab compared with axitinib (HR for death: 0.61) and BSC (HR for death: 0.44).

The expected number of patients with advanced RCC who have received prior therapy in England for 2017 is estimated at 1,823. As noted previously, it should be acknowledged that this estimate should be treated with caution as it does not incorporate prevalence data or accommodate for death within the first year of diagnosis (despite active treatment).

Table 27: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: <12 months with BSC; <24 months with established standard of care Source: population studies[52, 53]; regulatory trial data [50, 51]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median survival times: Nivolumab: 25.0 months Current NHS treatment: ≤20 months Between group difference: ≥5.0 months Source: AXIS trial data[50]; CheckMate 025 trial data[71]; RECORD-1 trial data[51]
The treatment is licensed or otherwise indicated for small patient populations	Advanced RCC population for 2016: 2,431 Maximum number of patients with advanced RCC who have received at least one line of prior therapy by 2017: 1,823 Source: Extrapolated ONS cancer registrations data for kidney cancer[54] ; reported rates of advanced RCC from literature base[15, 16, 18, 56-59]; clinical expert consultation[45, 60]
Key: BSC, best supportive care; NHS, National Health Service.	

4.14 Ongoing studies

Additional evidence from trials presented in this submission to support the use of nivolumab for the treatment of advanced RCC patients who have received prior

therapy is likely to become available in the next 12 months, as summarised in Table 28.

Table 28: Additional evidence availability

Study	Additional evidence	Expected date of availability
CheckMate 025	2-year OS data	ESMO 2016
CheckMate 010	4-year OS data	ASCO 2016
CheckMate 003	5-year OS data[a]	ASCO 2016
Key: AIC, academic in confidence; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; OS, overall survival. **Notes**: [a], available and therefore presented in this submission as AIC		

A Phase IIIb/IV safety trial of nivolumab monotherapy in previously treated advanced RCC patients is also currently recruiting patients (CheckMate 374; NCT02596035). The primary objective of this trial is to generate safety data by the assessment of high grade immune-mediated adverse events in this patient population. In addition to continuing the investigation of safety for RCC patients with clear cell histology and prior treatment with antiangiogenic therapy, this study will explore the safety and efficacy data for RCC patients with non-clear cell histology and RCC patients with either histology and brain metastases. Results will not however be available until 2018.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

An up-to-date systematic literature review of previous cost-effectiveness studies was not completed in time for this submission. Nevertheless, a systematic review of previous cost-effectiveness studies in previously treated, advanced RCC was reported in the manufacturer's submission dossier for the most recent technology appraisal in this indication (TA333: Axitinib for treating advanced RCC after failure of prior systemic treatment, guidance published February 2015, literature searches performed June 2012).

There is an established paradigm of Markov modelling with health states to capture the key clinical outcomes of disease progression and death, in previously treated, advanced RCC.[109] In TA333, the manufacturer submitted a three-state Markov model (pre-progressive disease, progressed disease, death), and the Evidence Review Group (ERG) were satisfied with the approach, which was "*consistent with other published economic studies of advanced renal cell carcinoma*".[61]

5.2 De novo analysis

5.2.1 Patient population

As described in Section 2.2, positive CHMP opinion on an EMA marketing authorisation application for use of nivolumab in adults with previously treated, advanced RCC was granted on 25th February 2016. The de novo economic analysis evaluates the cost effectiveness of nivolumab in this patient group.

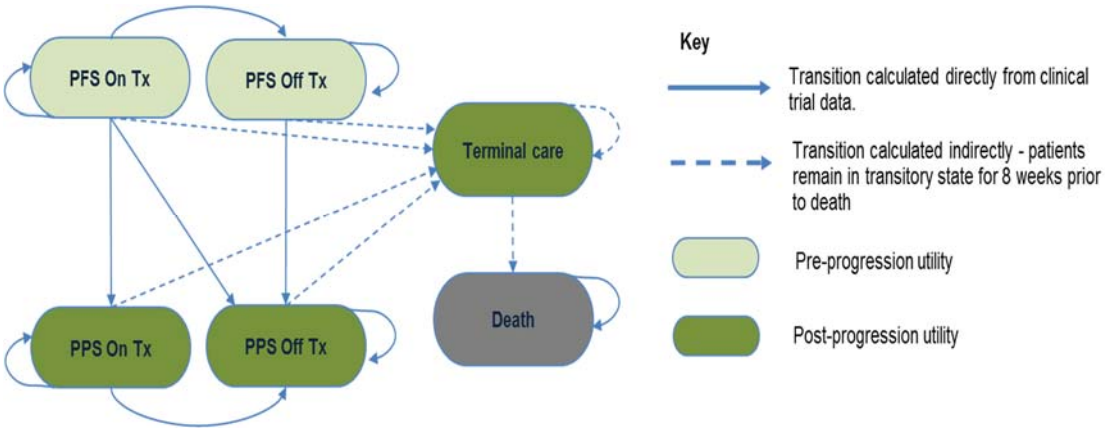
The key clinical data available for the submission are from CheckMate 025, described in detail in Section 4, which assessed nivolumab versus everolimus in patients who had received one (72%) or two (28%) previous antiangiogenic therapies. These data, from a robustly designed, controlled study, are useful to inform the economic comparison of nivolumab versus everolimus. Comparisons to other care options for previously treated advanced RCC patients in England, axitinib and best supportive care, are supported by results from network meta-analyses, described in Section 4.10.

5.2.2 Model structure

A de novo economic model was constructed to evaluate the cost-effectiveness of nivolumab; its structure and possible patient transitions are represented diagrammatically by Figure 23. In line with previous studies and TA333, a Markov model is used, with health states to capture the key clinical outcomes of disease progression and death.

As shown in Figure 23, the de novo model comprises six health states. These health states capture treatment status as well as disease progression, and are consistent with the care pathway and treatment-dependent costs and outcomes associated with each component. As patients receive active therapy, they incur treatment-specific drug, administration, resource use and adverse event costs.

Figure 23: Economic model health states and structure



Key: PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

As described in Section 4.3, owing to the immune-system-stimulating mechanism of nivolumab, CheckMate 025 allowed treatment beyond RECIST-defined progression if they were believed by the investigator to be experiencing clinical benefit and tolerating treatment. In line with the label for everolimus, these treatment rules were also applied to patients randomised to everolimus. As a result, patients on either arm of Checkmate 025 could and did discontinue therapy before or after disease progression, and model states are sufficient to capture this.

Evidence from analysis of patient-level EQ-5D data from CheckMate 025, presented in Section 5.4.1, suggests that patient HRQL differed by disease progression status,

consistent with patient EQ-5D data used in TA333 and previous studies, and also treatment arm, consistent with the different mechanism of action and response rates across nivolumab and everolimus. The model structure is sufficient to capture such outcome differences.

Before and after disease progression, advanced RCC patients receive disease management including health professional visits, tests and scans; the model captures the NHS/PSS costs associated with these resources and how they differ by progression status.

It is possible to transition to death from any of the disease- and treatment-related health states, via the transitory “Terminal care” health state.

Research from The King’s Fund [110] has estimated the economic burden of palliative care in the 8 weeks preceding death; this estimate has been used in TAs previously, for example, in NICE TA268, as a relevant data source. To account for this cost, the proportion of patients in “PFS On Tx”, “PFS Off Tx”, “PPS On Tx”, “PPS Off Tx” is adjusted in the model to account for the proportion of patients expected to be receiving palliative care (defined in line with the period over which palliative care costs were estimated [110] as 8 weeks prior to death). Transitions to the “Palliative Care” model state are described as “indirect” in Figure 23.

Additional key features of the economic model are described and justified in Table 29.

Table 29: Features of the de novo analysis

Factor	Chosen values	Justification	Reference
Time horizon	30 years	Mean age of patients in CheckMate 025 was 62 years; over 99% of patients in any model arm are dead at 30 years	Extrapolation of OS from Study 025 and application of NMA results
Cycle length	1 week	Sufficiently short to accurately capture clinical outcomes in CheckMate 025 and comparator trials and fit with dosing schedules	Sections 5.3 and 5.5
Half-cycle correction	Not applied	The cycle length is short	Sonnenberg (1993) [111]
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case	NICE (2013) [112]
Discount of 3.5% for utilities and costs	3.5% per annum	NICE reference case	NICE (2013) [112]
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE (2013) [112]

Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, Overall survival; NMA, Network meta-analysis; PSS, Personal social services; QALYs, Quality-adjusted life years.

5.2.3 Intervention technology and comparators

In line with the final scope, the comparators for nivolumab in people with previously treated advanced RCC are everolimus, axitinib and BSC.

Nivolumab and everolimus are implemented in the model as per the dosing schedule in CheckMate 025, and as described in Section 2.3. On the intervention arm, nivolumab was administered at a dose of 3mg/kg by intravenous infusion every two weeks; on the comparator arm, everolimus was administered orally at a daily dose of 10mg.

Time to treatment discontinuation (TTD) data from CheckMate 025 were used to inform the model. Parametric survival curves estimated from CheckMate 025 data

show the duration of treatment to be different to PFS across both study arms, and particularly on the nivolumab arm, where treatment continued substantially beyond progression for some patients (see Figure 39, Section 5.3).

In line with the SmPC and key clinical data for axitinib, the model assumes the recommended dosing schedule of 5mg administered orally twice daily, but accounts for relative dose intensity observed in the AXIS study (102.0%; owing to dose increases in 36.8% of patients and reductions in 30.8% of patients). In the absence of patient TTD data for axitinib in previously treated RCC patients, and in line with the license for axitinib, treatment was assumed to continue to progression for patients in the axitinib arm of the model.

There are no treatment costs assumed for patients in the BSC arm of the model.

5.3 Clinical parameters and variables

As described in Section 5.2, the pivotal study to inform the cost-effectiveness analysis was CheckMate 025, described in detail in Section 4.

The following clinical outcomes were assessed:

- OS
- Investigator-assessed PFS
- TTD
- HRQL (reported in Section 5.4)
- TRAEs (reported in Section 5.4)

Parametric survival analyses of OS, PFS and TTD data from CheckMate 025 inform the proportion of patients in each model health state in each cycle in the nivolumab and everolimus arms of the model. To inform the proportions of patients in each model cycle in axitinib and BSC model arms, HRs for PFS and OS from NMA analyses described in Section 4.10 are applied to the everolimus survival curves.

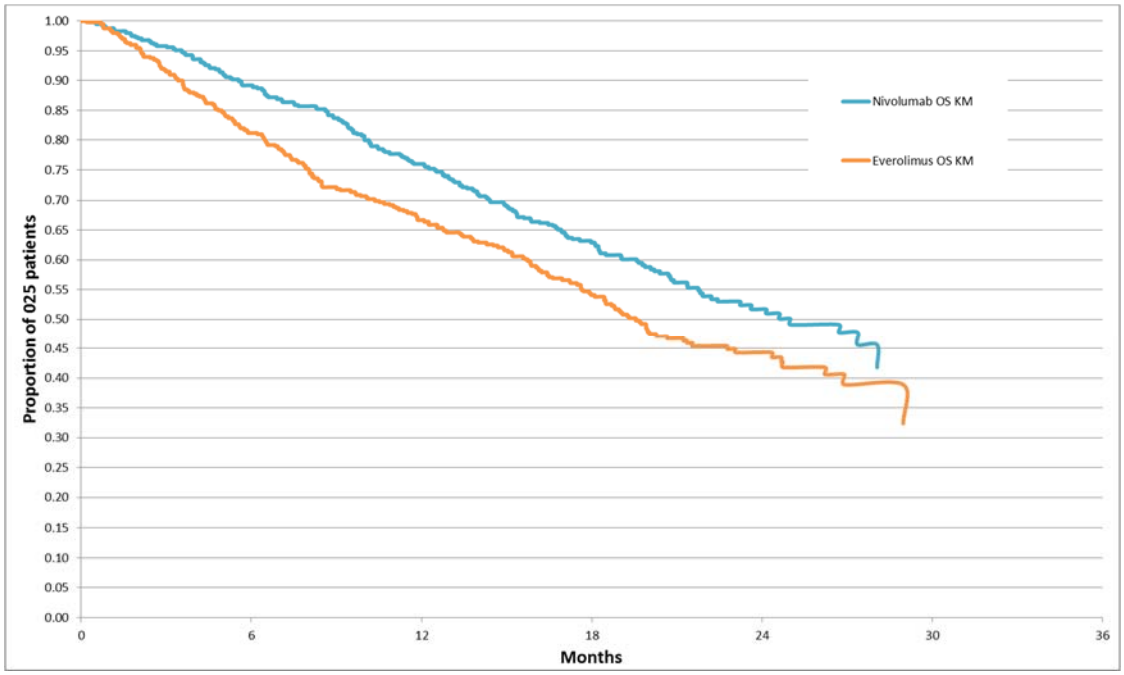
The remainder of Section 5.3 describes the methodology and results of parametric survival analyses to capture and extrapolate OS, PFS and TTD data from

CheckMate 025 over a lifetime horizon, and incorporation of NMA results to estimate OS and PFS curves for axitinib and BSC.

5.3.1 Overall survival

Figure 24 shows KM OS data for CheckMate 025 patients; Table 30 shows number at risk, over time. Due to the incomplete nature of these data, and diminishing number at risk towards the end of the curve, fitting parametric models to the data was necessary, following guidance in NICE Decision Support Unit Technical Support Document (DSU TSD) 14.[113]

Figure 24: KM OS data, CheckMate 025



Key: KM, Kaplan-Meier; OS, overall survival.

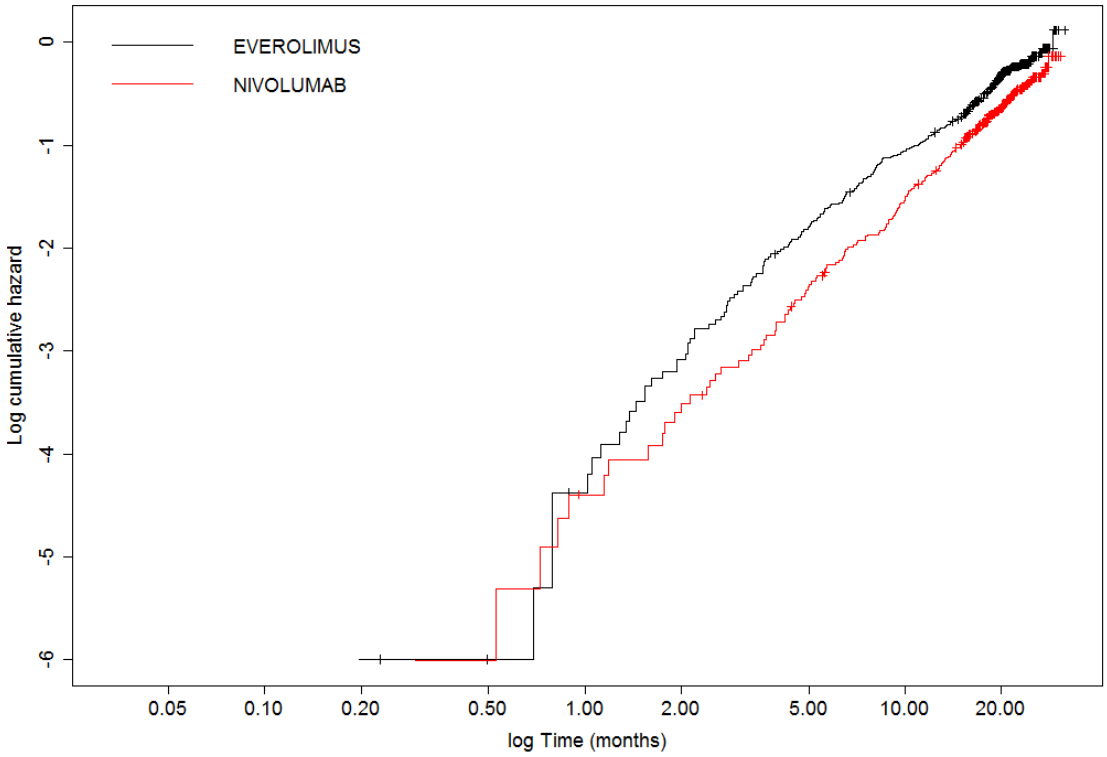
Table 30: Number at risk over time, overall survival, CheckMate 025

Months	0	3	6	9	12	15	18	21	24	27	30	33
NAR - Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
NAR - Everolimus	411	366	324	287	265	241	187	115	61	20	2	0
Key: NAR, number at risk												

The assumption of proportional hazards (PH) in OS KM data was tested, to assess whether survival analysis stratified by treatment group was appropriate. Figure 24

and Figure 25 suggest PH across treatment arms in CheckMate 025. Survival analyses for OS were therefore performed using the un-stratified OS data.

Figure 25: Log cumulative hazard plot, OS in CheckMate 025



Key: OS, overall survival.

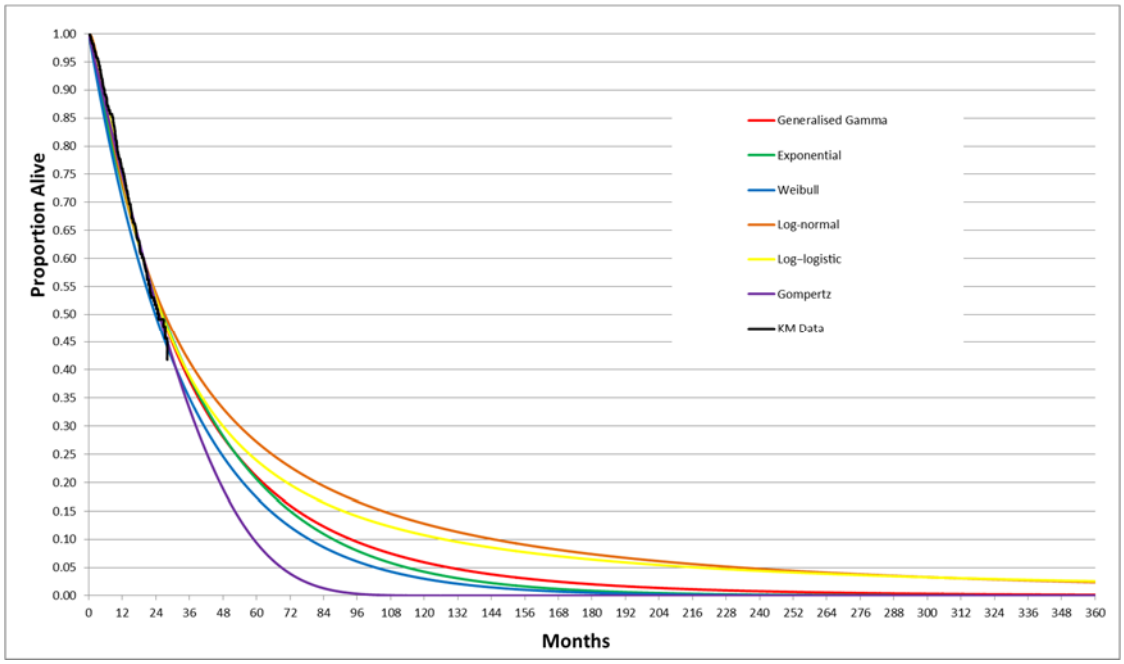
Curves were fitted to the complete OS dataset using the six parametric model forms recommended for consideration in DSU TSD 14 (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised Gamma) [113], and the fit of each parametric model was compared with the observed data. The most appropriate functional form was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics. These measures provide an indication of the statistical fit between the observed KM data and the parametric model estimates throughout the trial period. The use of AICs and BICs in the selection of the most appropriate curve has been criticised on the basis that they do not provide any measure of the relative merits of each functional form when used for extrapolation [113]. This is a valid criticism when extrapolation of data is required, and given the extent of extrapolation required, the plausibility of different extrapolations was assessed by visual inspection, by oncologists currently practising within the NHS in England and Wales, in three separate interviews [102], as described in Section 5.10.1.

Figure 26 and Figure 27 show six parametric model fits to the respective treatment arms of CheckMate 025; Table 31 reports AIC and BIC statistics for these model fits. By AIC and BIC statistics, the log-logistic model provides the best fit to the data.

To validate extrapolation assumptions, clinicians were shown the log-logistic curve fit to the everolimus data, with the rationale that their experience of patients with this established treatment was greater than their experience of long-term survival for nivolumab patients. They were then asked if this matched their expectations for previously treated patients who receive everolimus, with reference to predicted 5-year survival of around 17.5% from the best fitting model according to AIC and BIC criteria in Table 31, the log-logistic model. Oncologists independently reported that the log-logistic extrapolations were too optimistic and independently estimated that expected 5-year survival for such patients treated with everolimus is realistically around 10-12%.[102] From Figure 27, generalised gamma and exponential model fits best approximate these 5-year survival expectations.

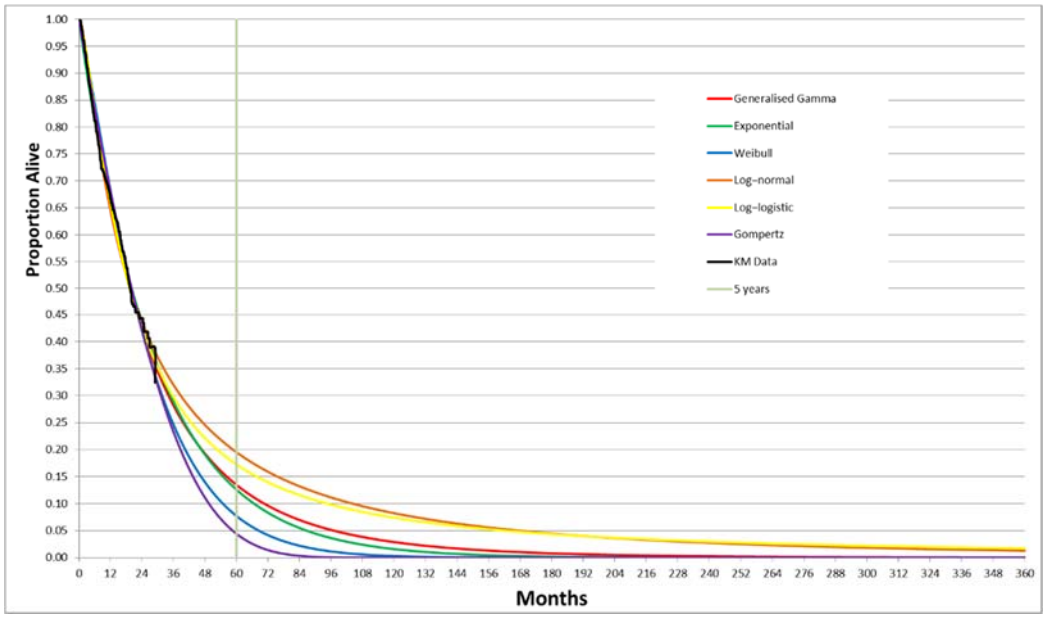
Owing to the importance of clinical plausibility when extrapolating beyond observed data, the generalised gamma model, which provides a better statistical fit to the KM data than the exponential model, is used in the base case.

Figure 26: Parametric model fits to un-stratified OS data from CheckMate 025, nivolumab arm



Key: KM, Kaplan-Meier; OS, overall survival.

Figure 27: Parametric model fits to un-stratified OS data from CheckMate 025, everolimus arm



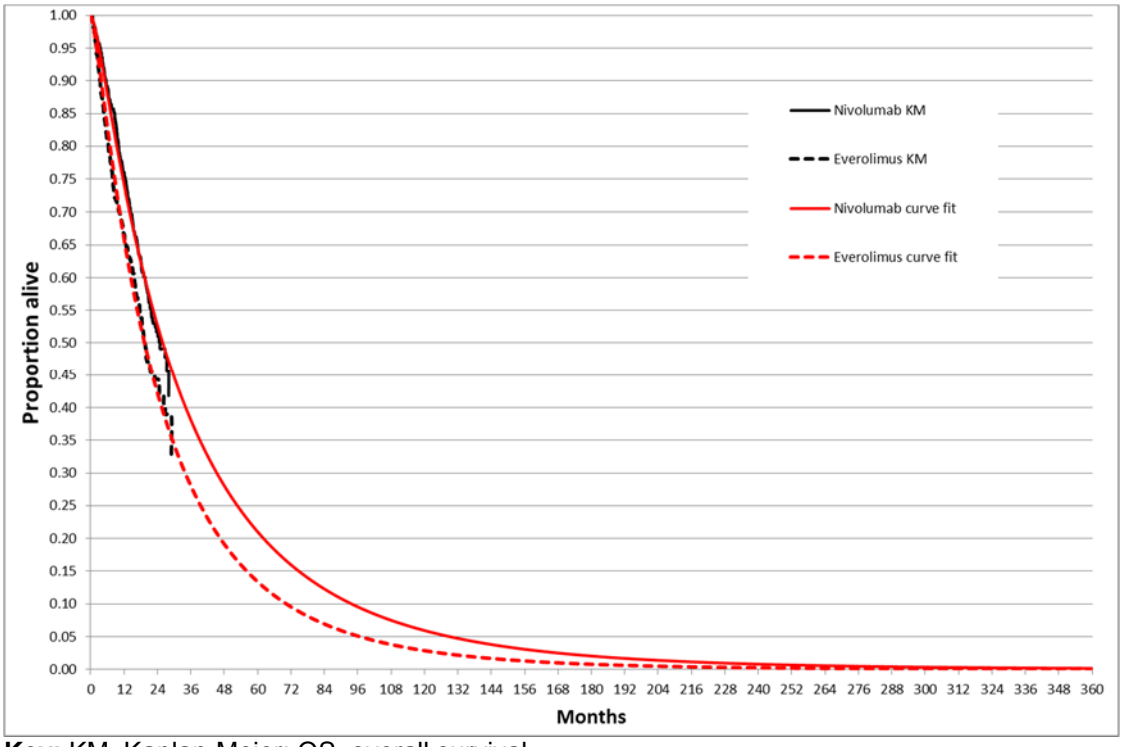
Key: KM, Kaplan-Meier; OS, overall survival.

Table 31: AIC and BIC statistics, Standard model fits to un-stratified OS data from CheckMate 025

Model	AIC	Model	BIC
Log-logistic	3564.866	Log-logistic	3578.998
Generalised gamma	3565.231	Weibull	3581.909
Weibull	3567.777	Log-normal	3583.784
Log-normal	3569.653	Generalised gamma	3584.073
Gompertz	3574.170	Exponential	3587.781
Exponential	3578.360	Gompertz	3588.301
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival.			

Figure 28 illustrates generalised gamma model curve fits to both arms of CheckMate 025 data, used to capture OS for nivolumab and everolimus.

Figure 28: Base case OS curve fits to CheckMate 025 data



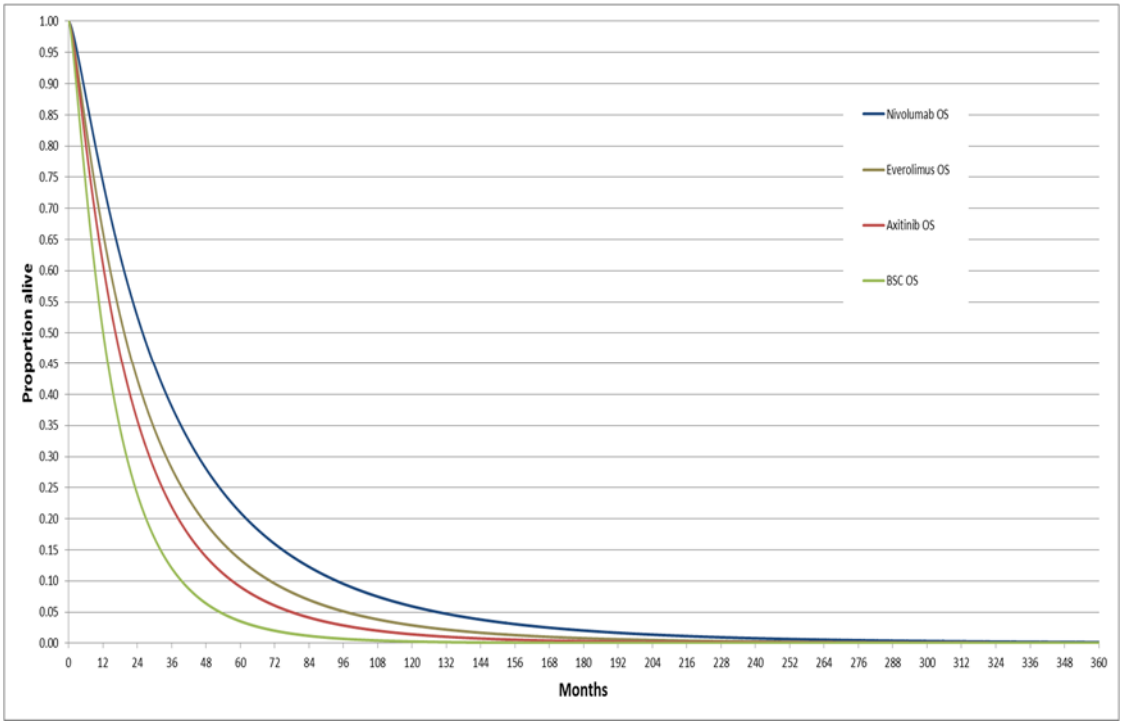
Key: KM, Kaplan-Meier; OS, overall survival.

When shown estimated survival curves for nivolumab alongside everolimus, clinicians were surprised not to see a long-term relative survival benefit for nivolumab, with anticipation of an immune-response-based plateau similar to that observed in melanoma patients treated with nivolumab (NICE ID845). One NHS oncologist predicted that a plateau beyond 30 months would be observed in practice if a study was powered appropriately, and estimated that approximately 20% of nivolumab treated patients will achieve long-term OS (beyond 5 years) and that after 5 years there would be a plateaued tail to the curve.

To account for clinical feedback, an alternative scenario for long-term nivolumab survival was explored. In addition to evidence from ID845, another immune-response therapy, ipilimumab, has demonstrated long-term survival comparable to age-matched general population estimates [114], while CheckMate 003 data recently reported 5-year survival of 34% (Section 4.11). Section 5.8.3 reports a scenario in which the risk of death for nivolumab patients who live to five years is assumed equal to the risk of death for the general population, calculated from the latest available Office for National Statistics (ONS) Interim Life Tables for England and Wales [115], adjusting for summary demographic characteristics of CheckMate 025 patients (mean age at model entry 62 years, 75% male).

To estimate OS for comparators outside of CheckMate 025, axitinib and BSC, HRs for everolimus versus axitinib and everolimus versus placebo, from NMA results reported in Section 4.10, were applied to the OS survival curve for everolimus. In the base case, in line with NICE DSU TD16, HRs from the crossover-adjusted NMA are used. The estimated OS curves for nivolumab, everolimus, axitinib and BSC are shown in Figure 29.

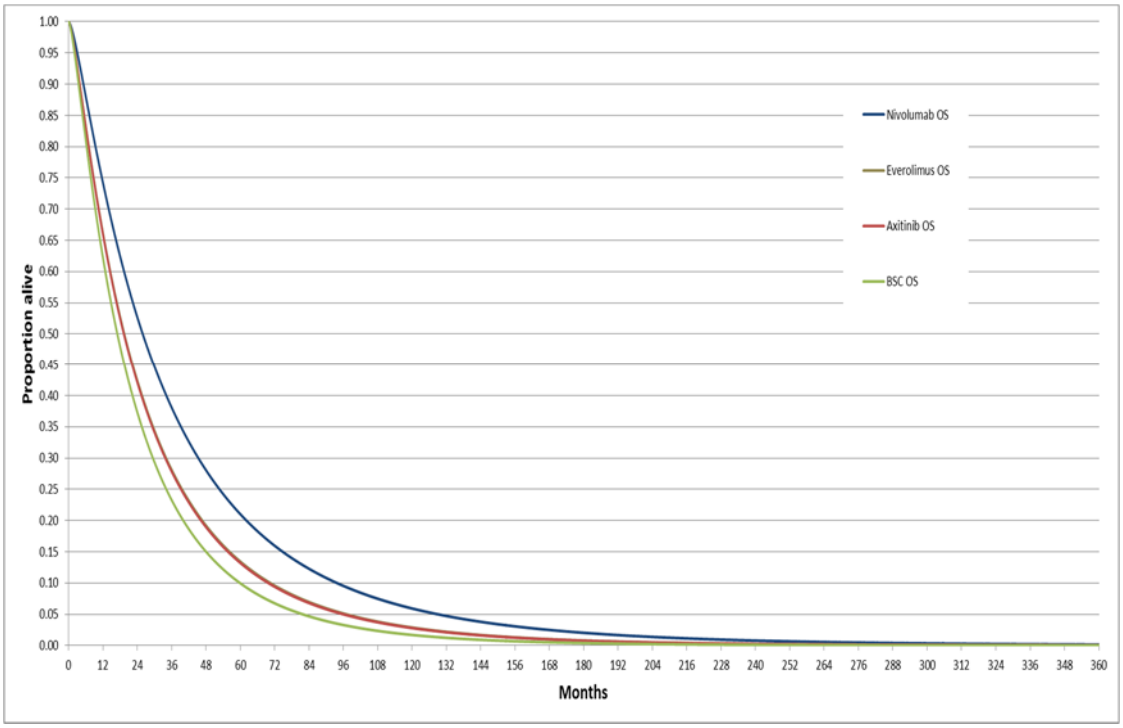
Figure 29: Base case OS curves, all treatment options



Key: BSC, best supportive care; OS, overall survival.

Reflective of NMA results in Section 4.10, Figure 29 predicts an OS survival benefit for everolimus versus axitinib. The crossover-adjusted NMA results are the most appropriate for analysis, following NICE DSU TSD16, and there is no head-to-head evidence comparing axitinib with everolimus in this indication. However, at clinical review, oncologists did not anticipate a survival advantage of everolimus over axitinib, while recently published evidence suggests similar progression-free survival across axitinib and everolimus in advanced RCC patients previously treated with sunitinib [103]. Figure 30 shows predicted OS using ITT NMA HRs to estimate survival for BSC and axitinib. A scenario using non-crossover-adjusted (ITT) NMA results is included in Section 5.8.3, to test the robustness of results to NMA assumptions. This scenario also serves to explore results when patients receiving axitinib and everolimus are assumed to have similar survival projections.

Figure 30: Scenario OS curves, using ITT NMA HRs

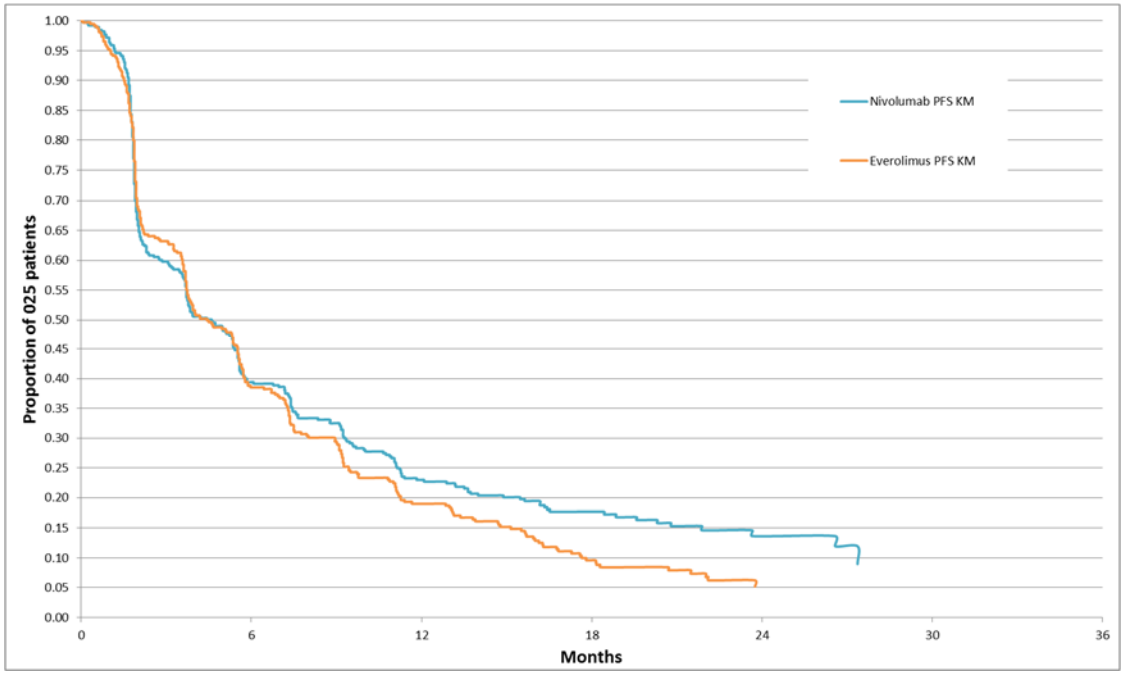


Key: BSC, best supportive care; OS, overall survival.

5.3.2 Progression-free survival

Figure 31 shows KM PFS data from Checkmate 025; Table 32 shows number at risk over time. In comparison to OS data, these data are far more complete, and while fitting curves to these data was necessary for extrapolation and due to diminishing numbers at risk at the foot of the curves, goodness-of-fit statistics are far more useful for curve selection.

Figure 31: KM PFS data, CheckMate 025



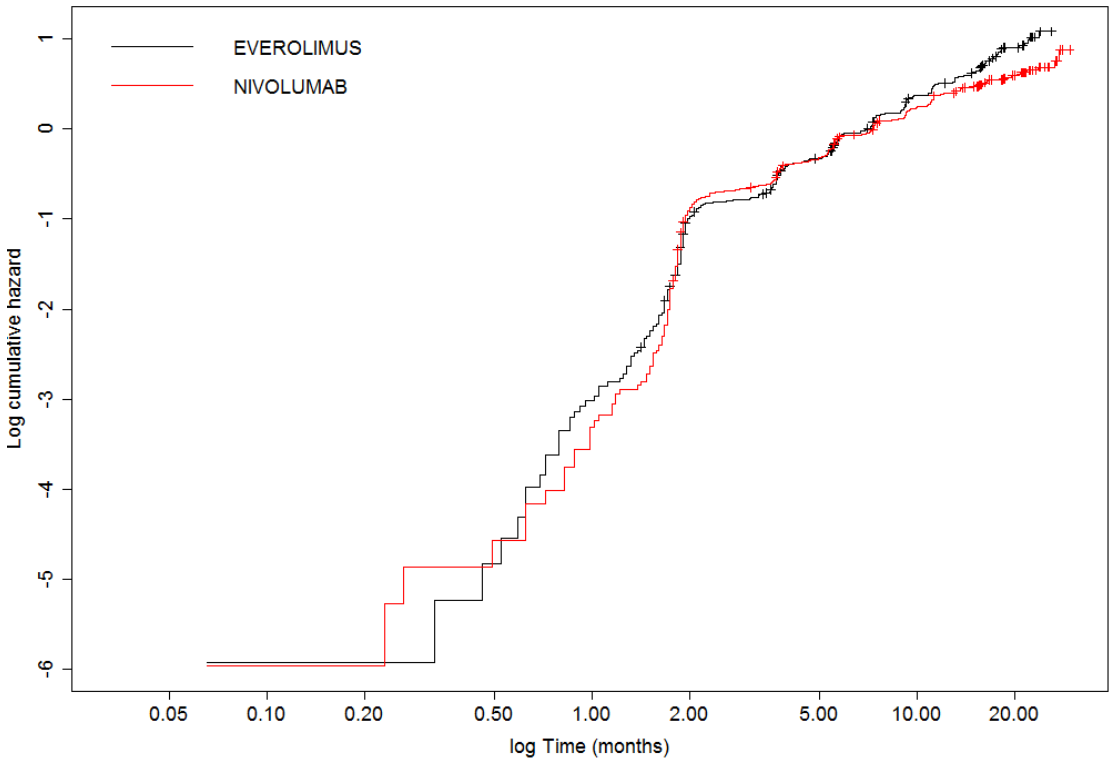
Key: KM, Kaplan-Meier; PFS, progression-free survival.

Table 32: Number at risk over time, progression-free survival, CheckMate 025

Months	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**
NAR - Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
NAR - Everolimus	411	227	129	97	61	47	25	16	3	0	0	0
Key: NAR, number at risk												

Figure 32 shows the log-cumulative hazard plot for PFS data in CheckMate 025. As described in Section 4.7, Figure 31 and Figure 32 illustrate that, unlike for the OS data, a PH assumption for PH data is not appropriate. As a result, parametric models were fit to PFS data stratified by treatment arm.

Figure 32: Log cumulative hazard plot, PFS in CheckMate 025

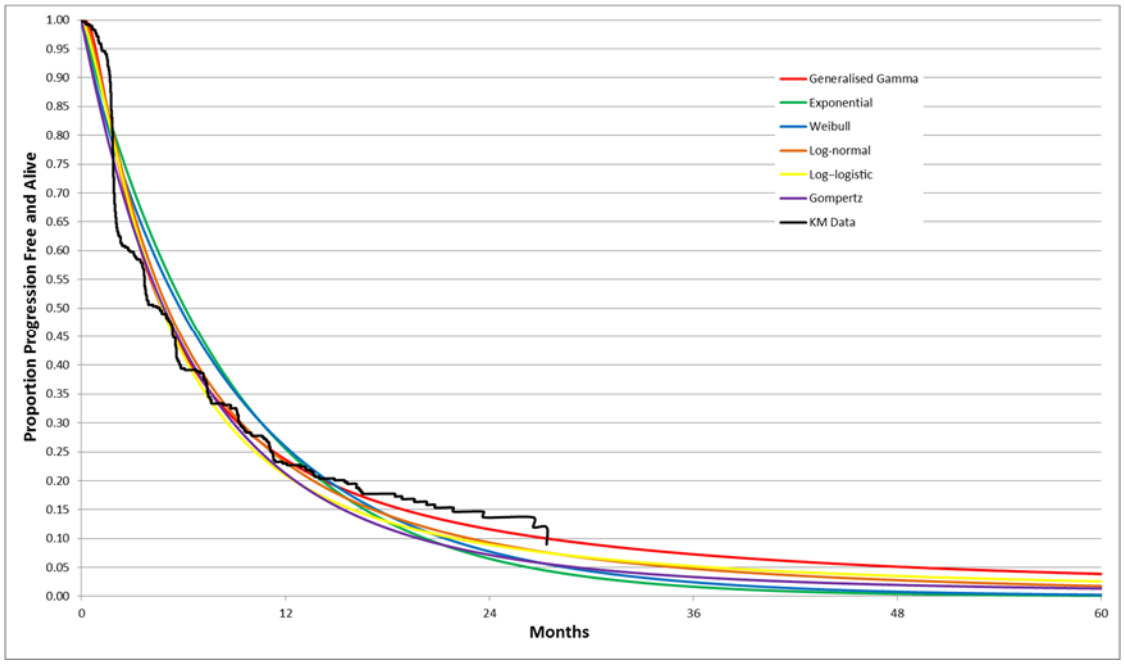


Key: PFS, progression-free survival.

Figure 33 and Figure 34 show the six standard parametric model fits to KM PFS data for nivolumab and everolimus. Table 33 and

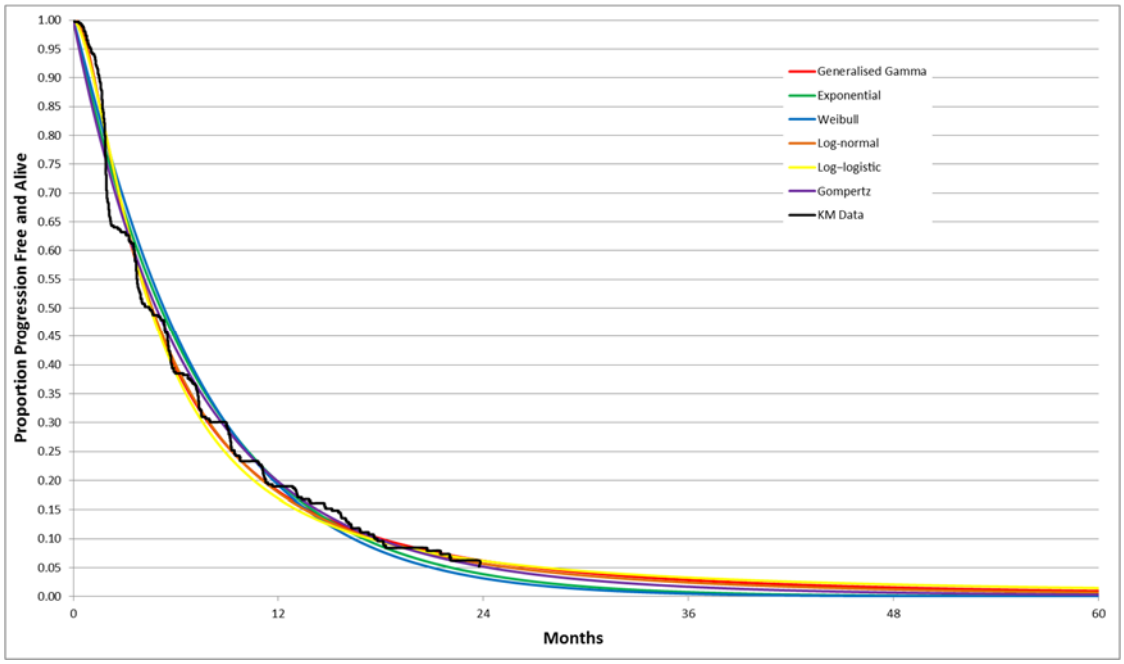
Table 34 show AIC and BIC statistics for these model fits. Across both arms, generalised gamma and log-logistic models provide the best statistical fit to the data, visually and by AIC and BIC statistics. However, owing to the sharp initial fall in PFS, particularly in the first 3 months of the nivolumab treatment arm, and subsequent flattening of the curve in these patients after around 12 months, none of these models are sufficiently flexible to fit the PFS data accurately.

Figure 33: Parametric model fits to stratified PFS data from CheckMate 025, nivolumab arm



Key: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 34: Parametric model fits to stratified PFS data from CheckMate 025, everolimus arm



Key: KM, Kaplan-Meier; PFS, progression-free survival.

Table 33: AIC and BIC statistics, Standard model fits to stratified PFS data, nivolumab arm, CheckMate 025

Model	AIC	Model	BIC
Generalised gamma	1932.912	Generalised gamma	1944.961
Log-normal	1944.538	Log-normal	1952.570
Log-logistic	1951.954	Log-logistic	1959.986
Gompertz	2006.797	Gompertz	2014.829
Weibull	2018.543	Exponential	2024.267
Exponential	2020.251	Weibull	2026.575
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.			

Table 34: AIC and BIC statistics, Standard model fits to stratified PFS data, everolimus arm, CheckMate 025

Model	AIC	Model	BIC
Log-normal	1887.522	Log-normal	1895.559
Generalised gamma	1888.860	Generalised gamma	1900.916
Log-logistic	1896.486	Log-logistic	1904.523
Gompertz	1933.468	Exponential	1937.581
Weibull	1933.491	Gompertz	1941.505
Exponential	1933.562	Weibull	1941.529
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.			

The steep drop in the early weeks of follow-up may be related to the timing of the first scan (8 weeks from randomisation) to assess PFS and may represent a subgroup of patients with poorer prognosis who are defined in accordance with RECIST criteria as progressing at point of first scan; potentially also reflecting patients with tumour flare (see section 2.1); whereas the flat tail at the end may be representing those patients with better prognosis and those whose disease stabilises following the initial tumour flare seen on the scan.

NICE DSU 14 highlights that spline-based models are less robust in structure than standard parametric models, and the former may be used when the latter are insufficiently flexible to fit the data accurately.[113] Parametric cubic spline models, "structurally flexible" extensions of the standard parametric distributions defined by piecewise polynomials joined at time-points along the curve (knots), were therefore explored.

Spline based models are particularly useful in this case as they can better fit the estimated KM data from clinical trials when the KM curves are "unique" and difficult to fit with standard distributions, or when several clinical processes influence the shape of the curve. In the context of nivolumab, spline based models provide a better fit to the observed data.

One advantage of spline-based models is they do not require the separation of survival data into independent sections (referred to as time-splitting). In previous technology appraisals, the time-splitting of data for piecewise modelling has been critiqued as the choice of time internals is always a point of contention. Piecewise modelling may also lead to a lack of correlation between adjoining curves – a recalculation of hazard ratios based on a shorter sample size that may also be non-randomised. In spline-based models, the time intervals for which the shape of the curve changes are defined by knots. Within the R *flexsurv* package that is used to fit the spline models to the KM data, a knot is placed at the first and last event (i.e. failure) observed within the survival data – referred to as the minimum and maximum knots. The number of intermediate knots placed within the minimum and maximum knot is then defined by the complexity of the survival curve, e.g. 2-knots spline (two intermediate knots) or 3-knots spline (three intermediate knots).

As spline based models are a novel technique to survival analysis the approach has been presented to various external health economists.[116] The general consensus across the experts was that, though spline-based models have not formally been part of previous technology appraisals, they are suitable in the context of nivolumab. It was agreed that due to the unique nature of the KM curves within immunotherapy spline-based models provide a statistically robust approach to modelling a complex dataset; these opinions are in line with the NICE DSU TSD 16 recommendations.

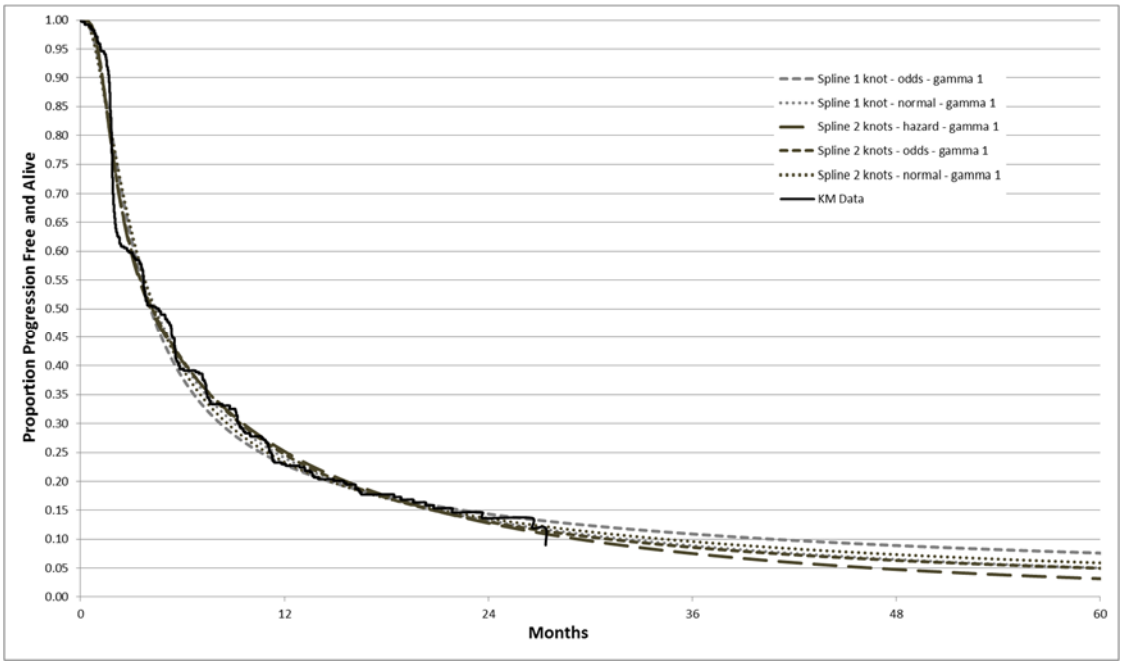
In addition, a key feedback received by the external health economists was that spline models above 2-knots would be at risk of being considered to “over fit” the data and would not have clinical plausibility. For example, a 5-knot spline model implicitly refers to potentially 6 different sub-groups within the data. It was considered anything more than 3 subgroups within the data (2-knot model) would be implausible and were therefore not considered.

Spline models were therefore tested with either 1 or 2 knots with three different potential functional forms for each modelled section – hazard, normal and odds.

Figure 35 and Figure 36 show various spline model fits to the data;

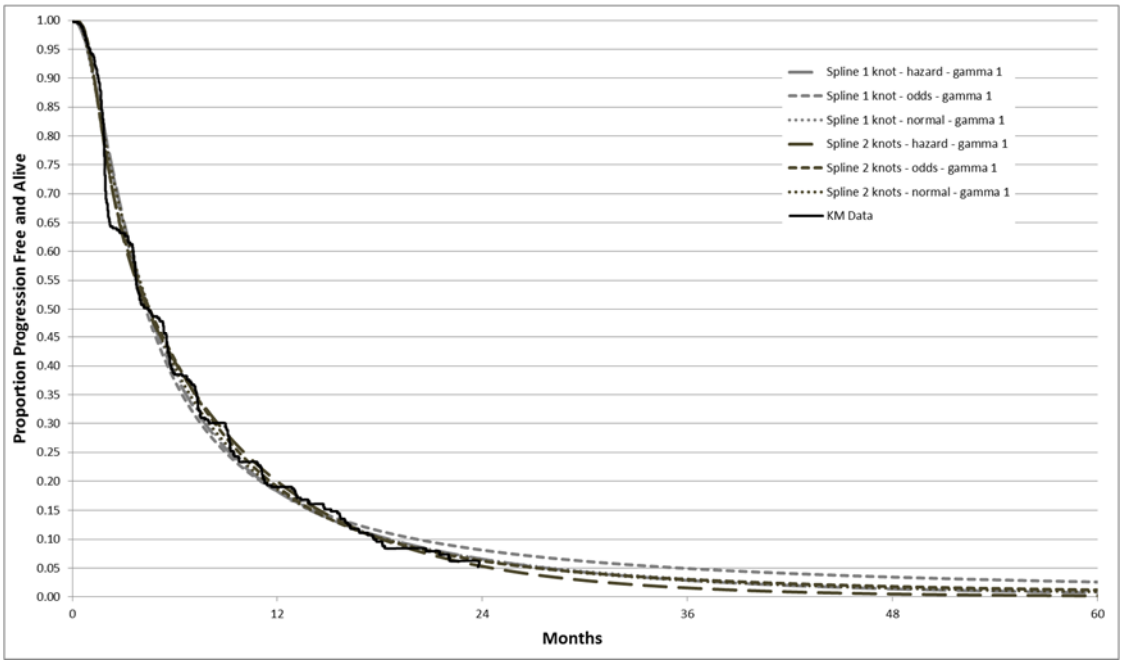
Table 35 and Table 36 show respective AIC and BIC statistics for these fits. One or two intermediate knots were used, implying two or three different patient groups with differing prognoses driving the initial sharp fall and later flattening in nivolumab PFS KM data. Visual inspection and goodness-of-fit statistics highlight the better accuracy of fit to the KM data than standard models, particularly for the nivolumab data. The spline odds 2-knot approach provides the best statistical fit to the data, and is used to model PFS in the base case.

Figure 35: Spline model fits to stratified PFS data from CheckMate 025, nivolumab arm



Key: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 36: Spline model fits to stratified PFS data from CheckMate 025, everolimus arm



Key: KM, Kaplan-Meier; PFS, progression-free survival.

Table 35: AIC and BIC statistics, Spline model fits to stratified PFS data, nivolumab arm, CheckMate 025

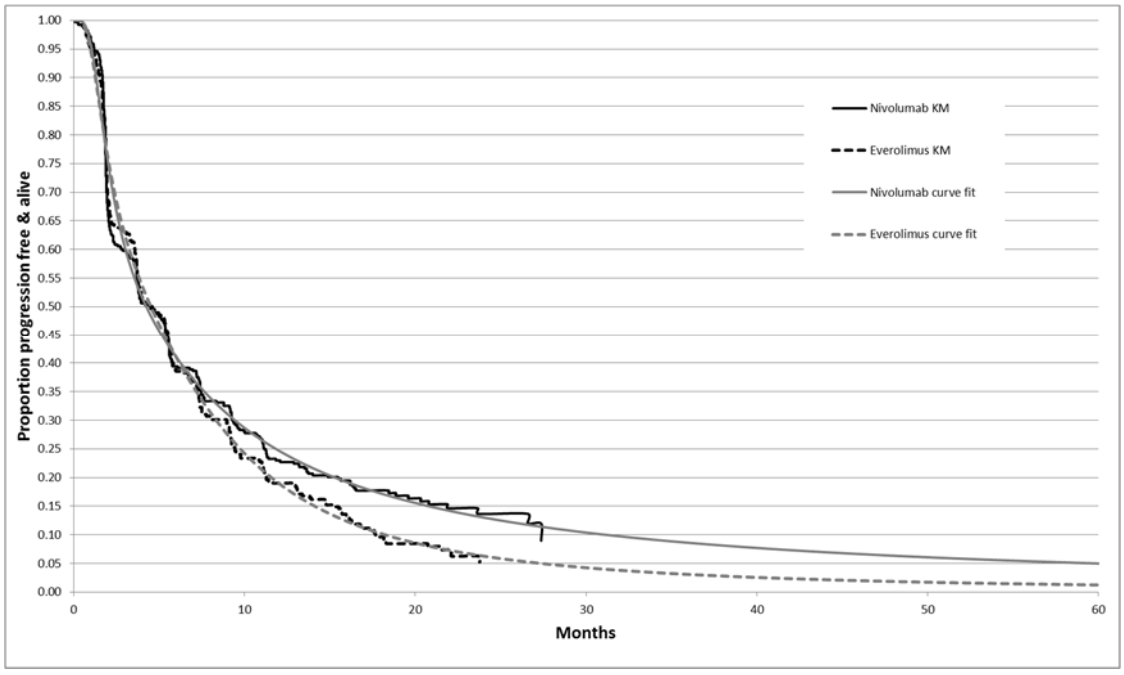
Model	AIC	Model	BIC
Spline 2 knot(s) - odds	1897.302	Spline 2 knot(s) - odds	1897.302
Spline 2 knot(s) - hazard	1897.665	Spline 2 knot(s) - hazard	1897.665
Spline 1 knot(s) - odds	1909.947	Spline 1 knot(s) - odds	1909.947
Spline 1 knot(s) - hazard	1915.430	Spline 1 knot(s) - hazard	1915.430
Spline 1 knot(s) - normal	1921.659	Spline 1 knot(s) - normal	1921.659
Spline 2 knot(s) - normal	1923.369	Spline 2 knot(s) - normal	1923.369
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.			

Table 36: AIC and BIC statistics, Spline model fits to stratified PFS data, everolimus arm, CheckMate 025

Model	AIC	Model	BIC
Spline 2 knot(s) - odds	1913.367	Spline 2 knot(s) - hazard	1889.731
Spline 2 knot(s) - hazard	1913.730	Spline 2 knot(s) - odds	1890.568
Spline 1 knot(s) - odds	1921.996	Spline 1 knot(s) - hazard	1899.088
Spline 1 knot(s) - hazard	1927.479	Spline 1 knot(s) - normal	1899.531
Spline 1 knot(s) - normal	1933.708	Spline 1 knot(s) - odds	1902.660
Spline 2 knot(s) - normal	1939.434	Spline 2 knot(s) - normal	1905.357
Key: AIC, Akaike Information Criterion; Bic, Bayesian Information Criterion; PFS, progression-free survival.			

Figure 37 shows base case PFS curves alongside the CheckMate 025 KM PFS data.

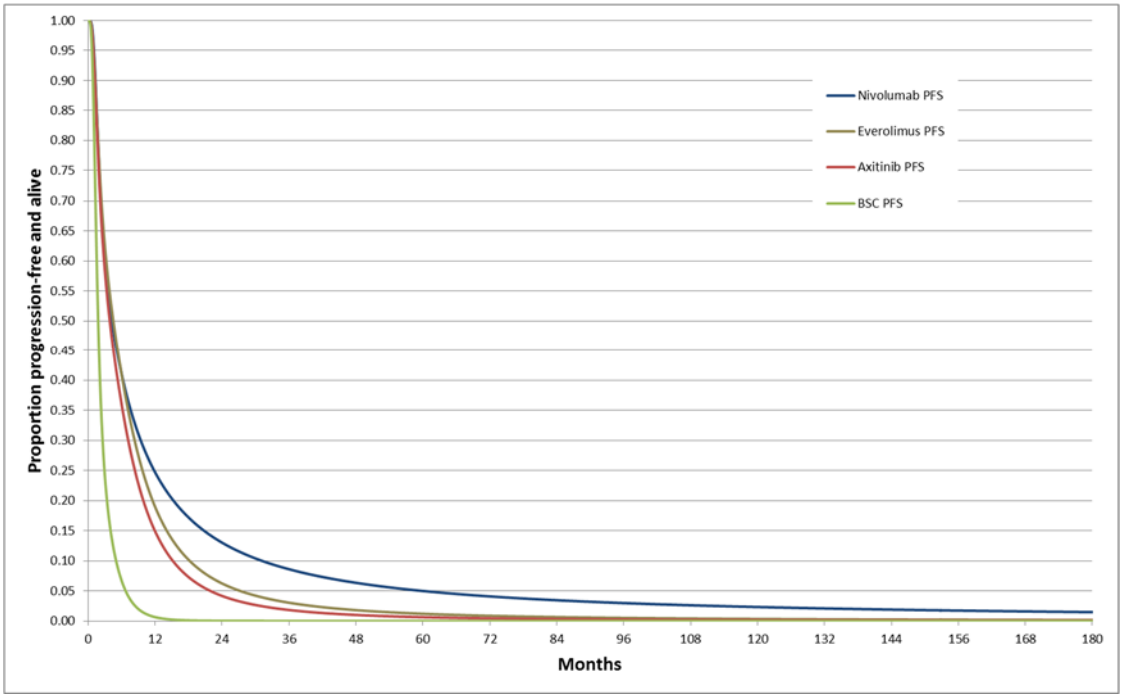
Figure 37: Base case PFS curve fits to CheckMate 025 data



Key: KM, Kaplan-Meier; PFS, progression-free survival.

In order to estimate PFS for comparators outside of CheckMate 025, axitinib and BSC, HRs for everolimus versus axitinib and everolimus versus placebo, from NMA results reported in Section 4.10, were applied to the PFS survival curve for everolimus. Figure 38 shows base case PFS curves across all treatment options.

Figure 38: Base case PFS curves, all treatment options



Key: PFS, progression-free survival.

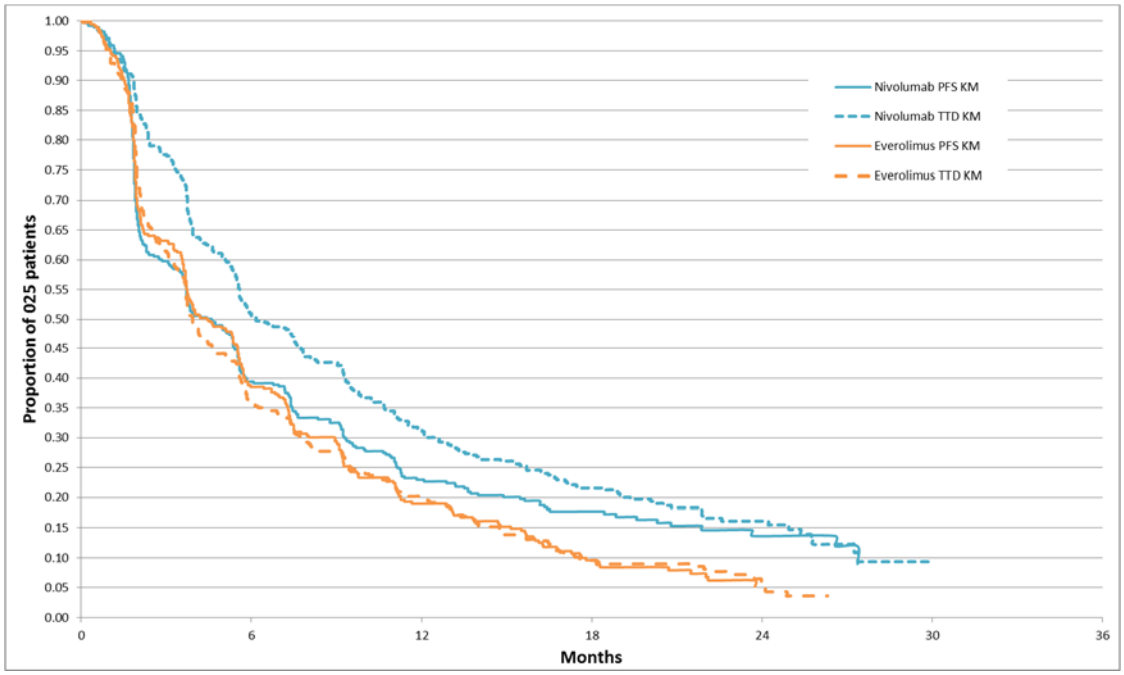
5.3.3 Time to discontinuation

Figure 39 shows KM TTD curves alongside KM PFS curves, from CheckMate 025. In order to accurately capture treatment acquisition and administration costs, survival curves were fitted to these TTD data. This was particularly important for the nivolumab arm, for which the TTD KM curve clearly followed a different trajectory to the PFS curve.

The KM TTD data, like the PFS data and unlike the OS data, are almost complete. As for PFS, while fitting curves to these data was necessary for extrapolation and due to diminishing number at risk at the foot of the curves, goodness-of-fit statistics are informative for curve selection.

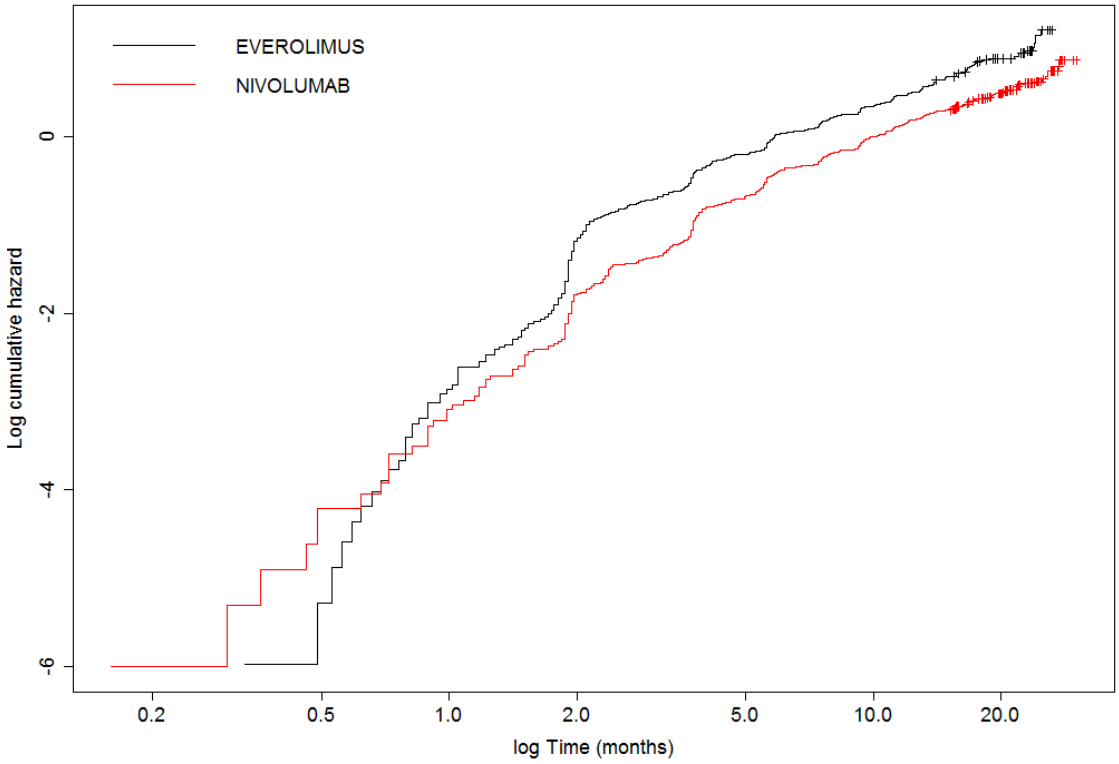
Figure 40 shows the log cumulative hazard plot for TTD in CheckMate 025. From Figure 39 and Figure 40, after initial separation, proportional hazards appears to hold across treatment arms of CheckMate 025. As such, single survival models were fit to the TTD dataset, un-stratified by treatment arm.

Figure 39: KM PFS and TTD data, CheckMate 025



Key: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

Figure 40: Log cumulative hazard plot, TTD in CheckMate 025



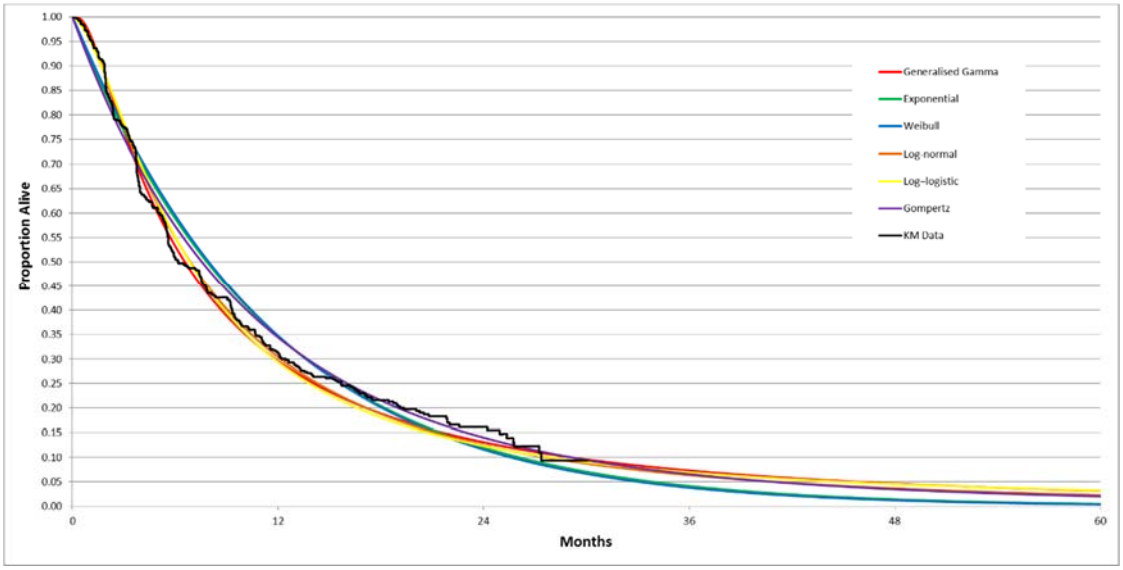
Key: TTD, time to treatment discontinuation.

Figure 41 and Figure 42 show standard parametric model fits to the un-stratified TTD data. Table 37 shows AIC and BIC statistics for these model fits. The standard parametric models provide a reasonable visual fit to the TTD data, compared to the PFS data. This is most true for the generalised gamma, log-normal and log-logistic curves, which also provide the best statistical fit.

However, on the everolimus arm, even the best fitting standard models struggle to fit the steep early curve and subsequent flattening also seen in the PFS data. Parametric cubic spline models were again explored as a more flexible alternative; Figure 43 and Figure 44 show various such spline models, assuming one or two knots, following the same rationale used in the PFS analysis. These models provide a better visual fit to the TTD data. Table 38 shows AIC and BIC statistics for the cubic spline models; comparison with Table 37 illustrates that the better-fitting of these models also provide a better statistical fit than the best-fitting standard parametric models.

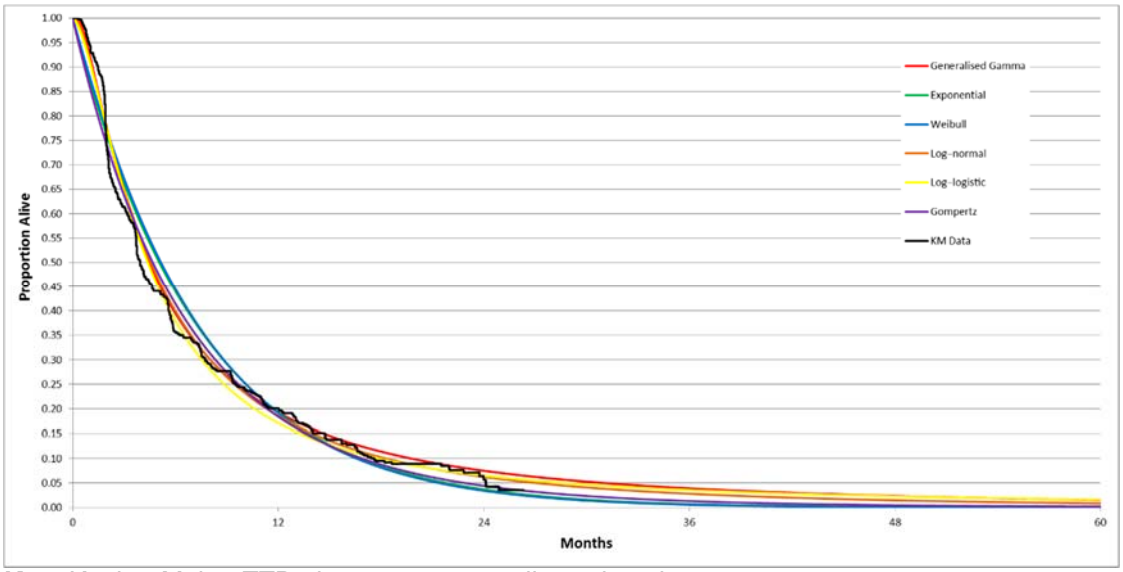
The spline hazard two knot approach provides the best statistical fit to the data, and is used to model TTD in the base case.

Figure 41: Parametric model fits to un-stratified TTD data from CheckMate 025, nivolumab arm



Key: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 42: Parametric model fits to un-stratified TTD data from CheckMate 025, everolimus arm

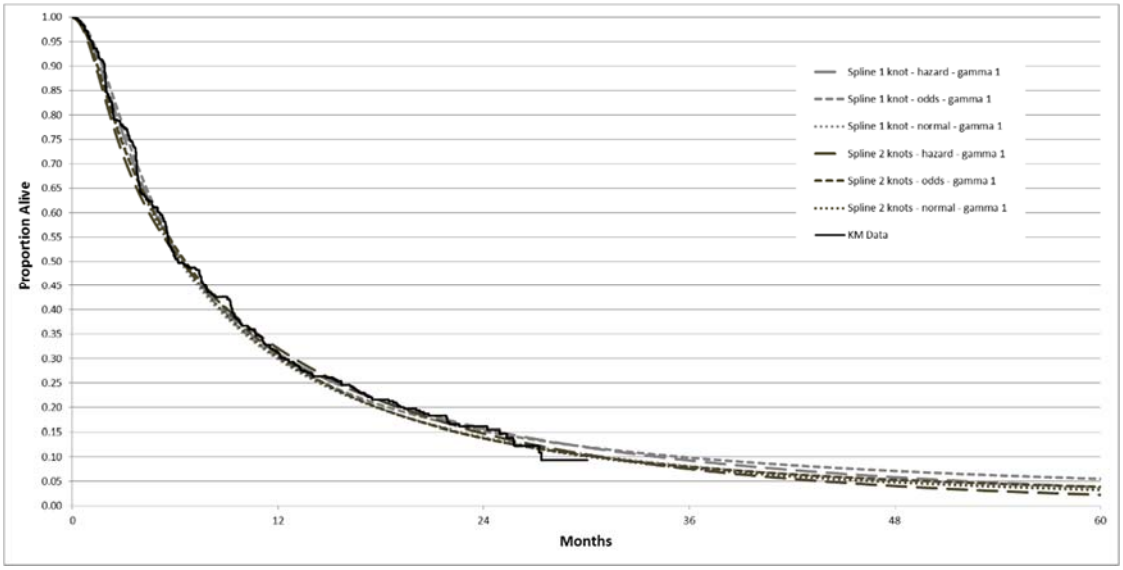


Key: Kaplan-Meier; TTD, time to treatment discontinuation.

Table 37: AIC and BIC statistics, Standard model fits to un-stratified TTD data, CheckMate 025

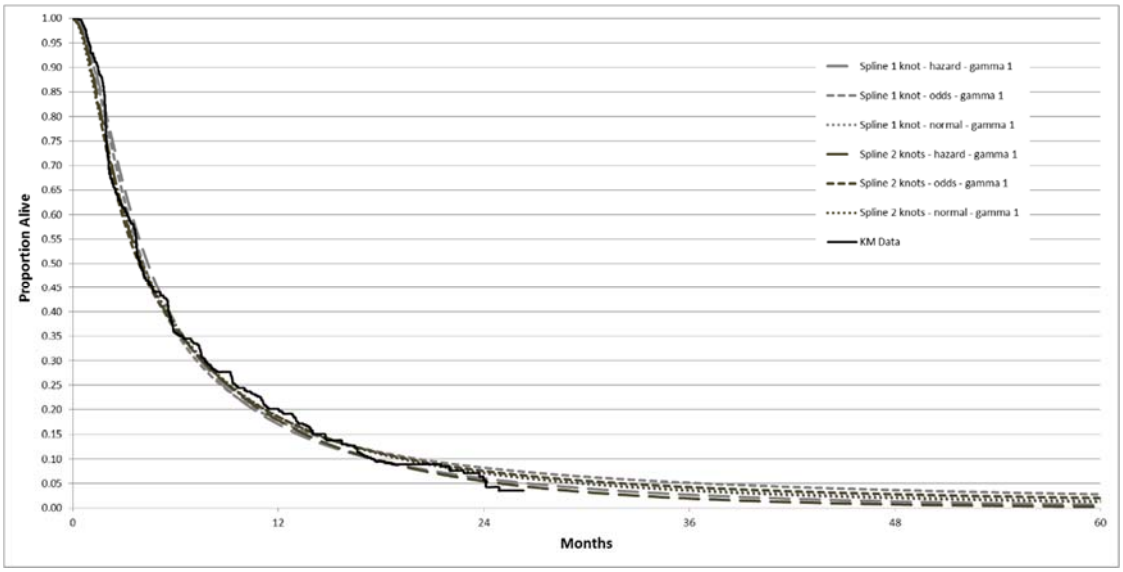
Model	AIC	Model	BIC
Generalised gamma	4429.807	Log-normal	4446.546
Log-normal	4432.481	Generalised gamma	4448.561
Log-logistic	4449.747	Log-logistic	4463.812
Gompertz	4525.747	Gompertz	4539.812
Exponential	4532.696	Exponential	4542.073
Weibull	4533.875	Weibull	4547.940
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TTD, time to treatment discontinuation.			

Figure 43: Spline model fits to un-stratified TTD data from CheckMate 025, nivolumab arm



Key: Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 44: Spline model fits to un-stratified TTD data from CheckMate 025, everolimus arm



Key: Kaplan-Meier; TTD, time to treatment discontinuation.

Table 38: AIC and BIC statistics, Spline model fits to un-stratified TTD data, CheckMate 025

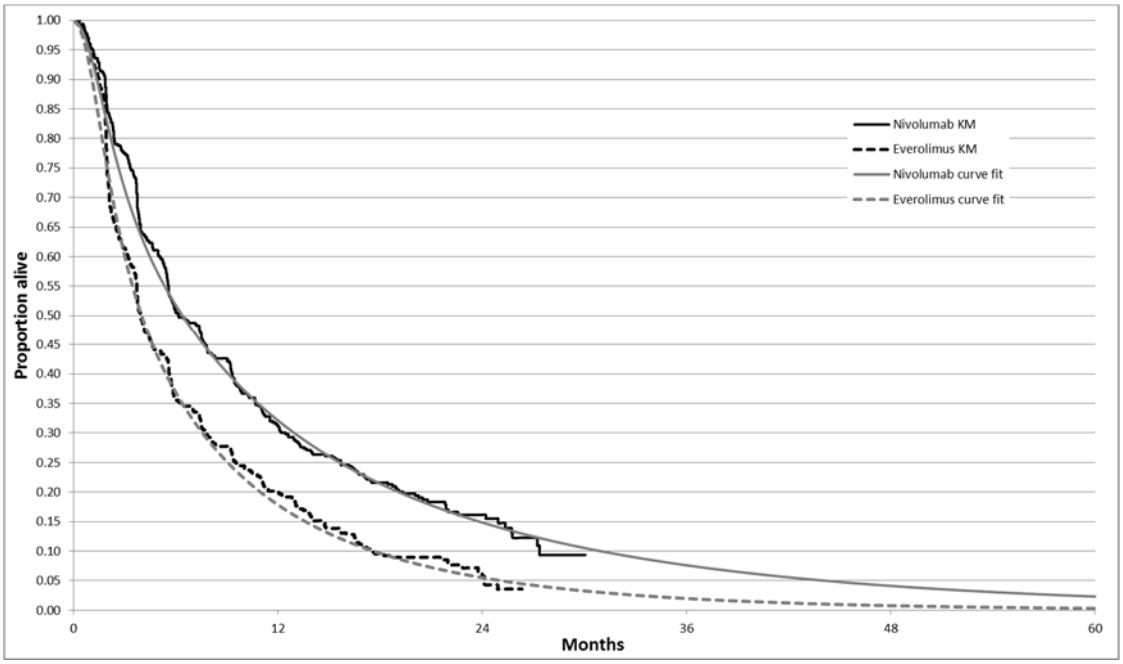
Model	AIC	Model	BIC
Spline 2 knot(s) – hazard	4415.016	Spline 2 knot(s) - hazard	4438.458
Spline 2 knot(s) - odds	4418.138	Spline 2 knot(s) - odds	4441.580
Spline 1 knot(s) – normal	4424.155	Spline 1 knot(s) - normal	4442.909
Spline 2 knot(s) – normal	4425.559	Spline 1 knot(s) - hazard	4444.513
Spline 1 knot(s) – hazard	4425.759	Spline 1 knot(s) - odds	4448.275
Spline 1 knot(s) - odds	4429.522	Spline 2 knot(s) - normal	4449.001
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TTD, time to treatment discontinuation.			

Figure 45 shows base case TTD curves alongside the CheckMate 025 KM TTD data.

In the base case, in the absence of TTD data for axitinib, axitinib treatment was assumed to continue until disease progression. This is discussed further in Section 5.5.2.

No treatment acquisition costs are applied to the BSC arm of the model; no TTD assumptions were necessary for this comparison.

Figure 45: Base case TTD curve fits to CheckMate 025 data



Key: Kaplan-Meier; TTD, time to treatment discontinuation.

5.4 Measurement and valuation of health effects

For patients with advanced, previously treated RCC, quality of life is known to be substantially affected by disease symptoms, including a lack of energy (fatigue), lack of appetite, and symptoms from metastatic disease, such as bone pain [66, 117]. Factors linked to treatment are also important for patient wellbeing; treatment-related toxicity is an issue in RCC management, while patient quality of life is affected by thoughts of the future, and how well their treatment is working [102 66].

5.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D questionnaire was completed in CheckMate 025; before any clinical activities, after randomisation, on Day 1 of each 4-week cycle, and at the first two follow-up visits (approximately 30 days and approximately 100-114 days after last dose). Assessments were performed prior to any study-related procedures. Compliance rates for EQ-5D completion were good across time-points, as shown in Table 39. The UK EQ-5D tariff was used to value patient questionnaire responses.

Table 39: EQ-5D Utility Index completion rate using all randomised subjects stratified by treatment, by visit

	Number of available patients at each visit		Number of patients with non-missing EQ-5D Utility Index scores[a]		Completion rate (%)[b]	
Visit	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**
Baseline	406	397	360	344	88.7	86.6
Week 4	386	371	335	314	86.8	84.6
Week 8	347	317	303	272	87.3	85.8
Week 12	316	246	267	220	84.5	89.4
Week 16	277	214	237	192	85.6	89.7
Week 20	244	176	209	158	85.7	89.8
Week 24	218	164	187	143	85.8	87.2
Week 28	193	139	164	122	85.0	87.8
Week 32	182	126	158	102	86.8	81.0
Week 36	172	114	145	97	84.3	85.1
Week 40	160	104	133	87	83.1	83.7
Week 44	144	94	120	74	83.3	78.7
Week 48	135	90	113	73	83.7	81.1
Week 52	123	78	98	63	79.7	80.8
Week 56	112	73	91	58	81.3	79.5

	Number of available patients at each visit		Number of patients with non-missing EQ-5D Utility Index scores[a]		Completion rate (%)[b]	
Visit	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**
Week 60	107	62	90	49	84.1	79.0
Week 64	105	58	82	44	78.1	75.9
Week 68	95	48	73	35	76.8	72.9
Week 72	84	42	64	30	76.2	71.4
Week 76	78	37	60	28	76.9	75.7
Week 80	71	33	54	24	76.1	72.7
Week 84	61	28	45	21	73.8	75.0
Week 88	55	23	44	15	80.0	65.2
Week 92	44	20	31	12	70.5	60.0
Week 96	37	19	30	12	81.1	63.2
Week 100	33	14	26	9	78.8	64.3
Week 104	26	10	20	9	76.9	90.0
Week 108	19	5	14	2	73.7	40.0
Week 112	15	2	12	2	80.0	100.0
Week 116	12	0	11	0	91.7	0.0
Week 120	5	0	3	0	60.0	0.0
Week 124	2	0	2	0	100.0	0.0
Week 128	1	0	1	0	100.0	0.0

	Number of available patients at each visit		Number of patients with non-missing EQ-5D Utility Index scores[a]		Completion rate (%)[b]	
Visit	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**	**Nivolumab**	**Everolimus**
Follow-up 1	318	333	189	167	59.4	50.2
Follow-up 2	264	269	161	135	61.0	50.2
Survival Follow-up 1	85	76	81	71	95.3	93.4
Survival Follow-up 2	72	69	68	64	94.4	92.8
Survival Follow-up 3	42	59	40	56	95.2	94.9
Survival Follow-up 4	29	44	29	42	100.0	95.5
Survival Follow-up 5	1	0	1	0	100.0	0.0
Survival Follow-up 6	5	19	5	18	100.0	94.7
Survival Follow-up 8	0	6	0	5	0.0	83.3
Survival Follow-up 10	0	1	0	1	0.0	100.0
Notes: [a], Number of patients having a non-missing EQ-5D Utility Index score; [b], Percentage of N out of the expected number.						

To account for autocorrelation of patient quality of life scores, and to understand how patient HRQL differed by treatment arm and progression status in Checkmate 025 patients, regression analyses were performed. A mixed model equation was fitted to the CheckMate 025 EQ-5D data, including fixed covariates for progression status (pre-progression/post progression) and treatment arm, a variable interacting treatment arm with progression status, and a random effect for subject.

Table 40 displays parameter estimates from this analysis. The estimate associated with the "Constant" parameter in Table 40, 0.798, is the point estimate of the utility associated with pre-progressive disease for nivolumab patients. This is slightly lower than the age-matched general population utility estimate from Ara and Brazier (0.817)[118]; this was at a level that was validated as sensible and expected by separate clinical experts with experience of nivolumab in this indication in England and Wales.[102]

The data suggest that significant negative consequences for patient utility associated with disease progression and receiving everolimus as opposed to nivolumab, independently. That disease progression had a negative effect upon utility is expected and in line with previous appraisals (Section 5.4.2) and practising oncologists' expectations [102]. The smaller, but significant, negative effect of randomisation to everolimus upon utility may be explained by lower response rates in the everolimus arm as compared with nivolumab. In addition, it is a reasonable assumption that knowledge of responding to study drug is likely to impact patient utility (Table 13, Section 4.7) for pre-progressive patients. For post-progressive patients, clinicians reported that higher utility is expected for nivolumab patients, due to both (i) treatment continuing beyond progression in many cases, and (ii) the immune-response mechanism of nivolumab that implies benefit beyond RECIST-defined progression and beyond treatment discontinuation.[102]

Table 41 summarises the CheckMate 025 EQ-5D utility estimates applicable to the model health states, to two decimal places, calculated using the data in Table 40. These data inform base case utility assumptions for nivolumab and everolimus arms of the economic model.

Table 40: Mixed model parameter estimates, CheckMate 025 EQ-5D data analysis

Parameter	Estimate	Standard error	P value
Constant	0.798	0.010	<.0001
Decrement - assigned to the comparator arm	-0.036	0.015	0.017
Decrement - disease progression	-0.069	0.007	<.0001
Decrement – interaction; disease progression and assigned to the comparator arm	0.005	0.010	0.654

Table 41: EQ-5D utility estimates by treatment arm and disease state, CheckMate 025

Health state	Treatment arm, CheckMate 025	
	Nivolumab EQ-5D utility estimate	**Everolimus EQ-5D utility estimate**
PFS	0.80	0.76
PPS	0.73	0.70
Key: PFS, progression-free survival; PPS, post-progression survival.		

5.4.2 Health-related quality-of-life studies

While it was not possible to perform a systematic review of the HRQL literature in time for this submission, data from TA333 are useful to inform and validate utility assumptions in this submission. From the manufacturer's systematic review (search date June 2012), patient-reported EQ-5D data in previously treated RCC are scarce [119, 120]; no patient-reported EQ-5D data in patients previously treated with non-cytokine therapy were identified.[109]

EQ-5D data were recorded in the AXIS study [66, 68]; estimates for mean on-treatment utility for axitinib patients and mean utility at treatment discontinuation were used to capture PFS and PPS utility, respectively, in the TA333 submission base case.[109] These estimates are shown in Table 42.

In their base case, the manufacturer assumed that the estimates in Table 42 were applicable for patients receiving either axitinib or BSC. The data were criticised by the ERG in TA333, as no information was provided on the valuation tariff used; the clinical study report indicated that the US EQ-5D tariff had been used; but nevertheless used in NICE's base case for decision making. The assumption that BSC patient utility was equivalent to axitinib patient utility was accepted as valid by the ERG, as disease symptoms were reasoned to balance against the toxicity profile of axitinib.

In this submission, for consistency with the NICE reference case and previous appraisals, the data in Table 42 are used to capture utility for patients in the axitinib and BSC model arms. However, the estimates in Table 42 are lower than those estimated for patients in either arm of CheckMate 025, in Table 41. One oncologist practicing in the UK NHS suggested that this was feasible due to the adverse event profile of axitinib in comparison to both everolimus and nivolumab, though the higher overall response rate associated with axitinib (19% in the AXIS study) in comparison to everolimus (5% in CheckMate 025; Table 13) could be expected to balance this out [102].

Table 43 shows alternative estimates for pre- and post-progressive previously treated RCC patients, used in a scenario analysis in TA333. Originally derived from a Phase II study of sunitinib in a cytokine-refractory patient population, these data were included for consideration in TA333 as they had been used in every previous NICE appraisal in second-line advanced RCC.[109] These estimates are closer to CheckMate 025 EQ-5D utility estimates for everolimus in Table 41.

To explore the importance of uncertainty regarding comparator utility assumptions in the comparisons to axitinib and BSC, two scenario analyses are considered in Section 5.8.3. One scenario assumes axitinib and BSC patient utility as described by

Table 43; another assumes patient utility in axitinib and BSC arms of the model are equal to utility reported by everolimus patients in CheckMate 025.

Table 42: Utility estimates, TA333 base case, from AXIS study EQ-5D data

Health state	Estimate	Source
PFS - TA333 base case	0.69	TA333; AXIS trial [109]- weighted mean on-treatment utility for axitinib patients
PPS - TA333 base case	0.61	TA333; AXIS trial [109]- mean utility at treatment discontinuation
Key: PFS, progression-free survival; PPS, post-progression survival.		

Table 43: Utility estimates, TA333 scenario, used in appraisals prior to TA333

Health state	Estimate	Source
PFS - TA333 scenario	0.76	TA333 [109] - previously used utility estimates in second-line advanced/metastatic RCC appraisals
PPS - TA333 scenario	0.68	TA333 [109] - previously used utility estimates in second-line advanced/metastatic RCC appraisals
Key: PFS, progression-free survival; PPS, post-progression survival; RCC, renal cell carcinoma.		

5.4.3 Adverse reactions

As described in Sections 5.4.1 and 5.4.2, patient-level EQ-5D data are used to capture HRQL across all model arms in the base case analysis, and the HRQL effects of treatment-emergent AEs are expected to be captured by these data.

Nevertheless, for thoroughness, treatment-emergent, Serious Grade III or IV AEs that occurred in at least 1% of patients in either treatment arm of CheckMate 025, reported in Section 4.12, are considered in a scenario in Section 5.8.3. These AEs and their assumed disutility values are shown in Table 44. A targeted search of the literature revealed few data on patient-reported utility decrements associated with these AEs in previously treated RCC patients. In the manufacturer's submission for pazopanib for first-line advanced RCC (TA215), utility decrements of -0.007 and -0.081 were used for Grade III/IV diarrhoea and anaemia, respectively [121]. Oncologists were aligned in their opinion that such a low disutility for Grade III/IV diarrhoea was inappropriate. One oncologist felt it would be reasonable in the absence of evidence to assume a decrement of -0.081 across AEs; yet another disagreed. For this oncologist, Grade III/IV diarrhoea had greater HRQL implications than Grade III/IV anaemia, while Grade III/IV pneumonitis had the worst implications

of the four, only marginally followed by Grade III/IV pneumonia. In order to avoid underestimating AE utility implications in this scenario, and in line with clinician feedback, the disutility estimates in Table 44 were used.

Table 44: AE utility decrement estimates

Serious Grade 3/4 AE	Utility decrement	Source
Pneumonitis	-0.15	Clinical validation of TA215 estimates[102, 121]
Diarrhoea	-0.10	
Anaemia	-0.08	
Pneumonia	-0.13	
Key: AE, adverse event.		

To capture the effect of these AEs on HRQL in this scenario, assumptions regarding the durations of AEs were required. Average duration of event information was recorded in CheckMate 025, and the data used are reported in Table 45.

Table 46 shows the QALY decrements associated with each event. To calculate this, the weekly QALY decrement associated with each event is multiplied by the median duration of event information in Table 45.

Table 45: Duration of AEs

Serious Grade III/IV AE	Median duration of AE (weeks)		Source
	Nivolumab	Everolimus	
Pneumonitis	2.71	3.14	CheckMate 025 Duration of event data; Pulmonary
Diarrhoea	3.21	3.00	CheckMate 025 Duration of event data; Gastrointestinal
Anaemia	4.21	4.21	CheckMate 025 Duration of event data; Hepatic[a]
Pneumonia	0.71	0.71	CheckMate 025 Duration of event data; Hypersensitivity/Infection[a]
Key: AE, adverse event. **Notes:** [a] Everolimus data were unavailable, assumed to be equal to nivolumab			

Table 46: QALY decrements per AE

Serious Grade III/IV AE	Utility decrement	Weekly QALY decrement	Nivolumab	Everolimus
			QALY decrement per event, weighted by duration of AE	QALY decrement per event, weighted by duration of AE
Pneumonitis	-0.150	-0.003	-0.008	-0.009
Diarrhoea	-0.100	-0.002	-0.006	-0.006
Anaemia	-0.081	-0.002	-0.007	-0.007
Pneumonia	-0.130	-0.002	-0.002	-0.002
Key: AE, adverse event; QALY, quality-adjusted life year.				

Finally, the cycle probability of each event, from CheckMate 025 incidence and time on treatment data, can be multiplied by the QALY decrement for each event to produce the cycle QALY decrement attributable to each AE for patients receiving treatment. These data are shown in Table 47 and Table 48. The resulting cycle QALY decrement is small for each arm of the trial; -0.000004 QALYs for the nivolumab arm and -0.000009 QALYs for the everolimus arm.

Table 47: Cycle probability of AE and cycle QALY decrement, nivolumab

Serious Grade III/IV AE	Event QALY decrement	Cycle Probability	QALY decrement per cycle
Pneumonitis	-0.008	0.001	-0.000005
Diarrhoea	-0.006	0.000	-0.000002
Anaemia	-0.007	0.000	-0.000001
Pneumonia	-0.002	0.000	0.000000
Total AE cycle QALY decrement, nivolumab			-0.000009
Key: AE, adverse event; QALY, quality-adjusted life year.			

Table 48: Cycle probability of AE and cycle QALY decrement, everolimus

Serious Grade III/IV AE	Event QALY decrement	Cycle Probability	QALY decrement per cycle
Pneumonitis	-0.009	0.001	-0.000011
Diarrhoea	-0.006	0.000	-0.000001
Anaemia	-0.007	0.001	-0.000005
Pneumonia	-0.002	0.001	-0.000001
Total AE cycle QALY decrement, everolimus			-0.000018
Key: AE, adverse event; QALY, quality-adjusted life year.			

For simplicity, in this scenario, the total cycle QALY decrement associated with Serious Grade III/IV AEs for axitinib patients is assumed to be equivalent to decrement for everolimus patients in Table 48.

5.4.4 Health-related quality-of-life data used in cost-effectiveness analysis

Table 49: Summary of utility values for cost-effectiveness analysis

State	Utility value	95% CI	Reference in submission	Justification
PFS, on treatment, nivolumab	0.80	Variance-covariance matrix from mixed model reported in Section 5.6.1	Section 5.4.1	CheckMate 025 EQ-5D data
PPS, on treatment, nivolumab	0.73			
PFS, on treatment, Everolimus	0.76			
PPS, on treatment, Everolimus	0.70			
PFS, axitinib	0.69	Beta (0.66,0.72)	Section 5.4.2	AXIS EQ-5D data; TA333
PPS, axitinib	0.61	Beta (0.58,0.64)		
PFS, BSC	0.69	Beta (0.66,0.72)	Section 5.4.2	Assumption upheld in TA333
PPS, BSC	0.61	Beta (0.66,0.72)		
Serious Grade III/IV AE				
Pneumonitis	-0.15	Beta (-0.12,-0.18)	Section 5.4.3	Medical oncologist opinion best available evidence
Diarrhoea	-0.1	Beta (-0.08,-0.12)		
Anaemia	-0.081	Beta (-0.07,-0.10)		
Pneumonia	-0.13	Beta (-0.11,-0.16)		

Key: AE, adverse event; BSC, best supportive care; CI, confidence interval; PFS, progression free survival; PPS, post-progression survival

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

While it was not possible to perform a systematic review of resource use and valuation studies in time for this submission, data from TA333, validated by medical oncologists currently working in the NHS, are useful to inform resource use assumptions in the model.

5.5.2 Intervention and comparators' costs and resource use

Table 50 displays the total estimated weekly drug acquisition cost for previously treated patients receiving nivolumab, everolimus and axitinib. Doses and treatment schedules are as described in Section 5.2.3. The unit drug costs of the treatments are based on the list price for nivolumab and all comparators.

Table 51 shows the estimated cost of intravenous administration associated with nivolumab treatment. Based on medical oncologist opinion, nivolumab is assumed to be administered in the NHS in an outpatient setting.[102]

To calculate the number of nivolumab vials required per administration for an average NHS England patient while accounting for wastage, patient-level weight data from CheckMate 025 patients based in Western Europe were used. Dosing based on the method of moments using patient weight data was applied to estimate the mean number of vials required in the base case. The method assumes a log-normal distribution for body weight and calculates the proportion of patients requiring each possible number of vials based upon the log-normal distribution derived from the individual patient weights. This calculation is an accurate method of accounting for wastage, assuming that no vial sharing occurs. The method has been used in recent ipilimumab and nivolumab NICE appraisals (TA319 and ID845).

The mean weight of Western European patients in CheckMate 025 was 80.93kg. Evidence from Ipsos Global Oncology Monitor suggests that the mean patient weight in UK clinical practice is far lower.[122] Assuming the same gender distribution as CheckMate 025 (75% male), the mean weight of Stage IV RCC patients treated between October 2014 and September 2015 was 72.45kg.[122] A scenario in Section 5.8.3 explores the implications of this patient weight for model results. In this scenario, in the absence of patient-level data from Ipsos Global Oncology Monitor, individual patient weights from CheckMate 025 Western European patients were multiplied by (72.45/80.93), in order to use the method of moments dosing approach applied in the base case.

Interviews with medical oncologists suggested that vial sharing in NHS England Oncology units may be viable, with consideration of feasible patient scheduling and the treatment of melanoma patients in the same unit as RCC patients.[102] To explore

the implications of vial sharing for model results, a scenario is explored in Section 5.8.3 in which the number of vials required for an average patient administration is calculated as the dose (3mg/kg) multiplied by the mean base case patient weight (80.93kg), divided by vial size (40mg or 100mg).

The proportion of planned nivolumab doses received was calculated from CheckMate 025 patient-level data as 92.425%, accounting for the proportion of doses delayed (5.075%; average dose delay was 14 days), and the proportion of doses omitted (2.5%). To calculate the proportion of planned everolimus doses received from patient-level data, the sum product of number of packs required to cover sum days of tablets received and maximum number of 28-day treatment pack cycles on treatment was calculated, as 94.240%. To account for the relative dose intensity observed for axitinib in the AXIS study and for consistency with TA333, as described in Section 5.2.3, the proportion of 5mg twice daily axitinib doses received by axitinib patients is assumed to be 102.0%.

Table 50: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators

Drug	Formulation (mg)	Cost per vial/ pack	Vials/ tabs per admin	Vials / tabs per pack	Dose	Unit	Treatments per week	Method	Proportions of doses received	Total cost per week	Source
Nivolumab	100	£1,097.00	1.73	1	3	mg/kg	0.5	IV	92%	£878.96	BMS
	40	£439.00	1.99	1						£402.79	BMS
Everolimus	10	£2,673.00	1.00	30	10	mg	7	Oral	94%	£587.77	MIMS[a]
Axitinib	5	£3,517.00	1.00	56	5	mg	14	Oral	102%	£896.84	MIMS[b]

Key: admin, administration; BMS, Bristol-Myers Squibb; IV, intravenous; MIMS, Monthly Index of Medical Specialties; Tabs, Tablets.
Notes: [1] (Antineoplastics - Afinitor) Accessed 20 January 2016; [2] (Antineoplastics - Inylta) Accessed 20 January 2016

Table 51: Intravenous administration cost

Administration costs, for nivolumab only	Unit Cost	Source
Administration of intravenous therapy	£186.53	NHS Reference Costs 2014-2015 Outpatient, Simple parenteral chemotherapy, Currency code SB12Z

Key: NHS, National Health Service.

5.5.3 Health-state unit costs and resource use

The base case resource use and unit cost estimates attributed to disease management are shown in Table 52. Resource use assumptions mirror those in TA333. The three NHS medical oncologists interviewed agreed broadly with TA333 disease management resource use assumptions, and estimates from TA333 are used in the base case. Feedback did however indicate that instead of monthly GP visits pre-progression, patients are seen by a Consultant at treatment administration (£189; NHS reference costs 2014-15; "Consultant led, first attendance, non-admittance, Code 370 - medical oncology", WF01B) (every 2 weeks for nivolumab, every 4 weeks for axitinib and everolimus), and that blood tests occur at every treatment administration. A scenario in Section 5.8.3 explores the impact of these alternative assumptions for analysis results.

Costs associated with resource use were updated to 2014/2015 NHS Reference or PSSRU costs, as reported in Table 52.

Table 52: Resource use and costs associated with model health states

Health states	Resource	Frequency per week	Source	Cost	Source
PFS	GP visit	0.25	TA 333	£37.00	PSSRU (2015) Section 10.8 p177, General practitioner - unit costs, Patient contact lasting 11.7 minutes, including direct staff costs, excluding qualifications
	CT scan	0.08	TA 333	£136.00	NHS reference costs 2014-15; "Diagnostic imagining, outpatient, CT scan more than 3 areas", RD27Z
	Blood test	0.25	TA 333	£3.00	NHS reference costs 2014-15; "Directly assessed pathological services - haematology", DAPS05
Total weekly cost associated with PFS health states					**£21.33**
PPS	GP visit	0.25	TA 333	£37.00	PSSRU (2015) Section 10.4 p172, Nurse specialist (community), 1 hour patient time, excluding qualifications
	Specialist community nurse visit	0.38	TA 333	£65.00	PSSRU (2015) Section 10.4 p172, Nurse specialist (community), 1 hour patient time, excluding qualifications
	Pain medication	7.00	TA 333	£5.30	TA333 (BNF section 4.7.2 Opioid analgesics (morphine sulphate 1 mg/mL, net price 5-mL vial = £5.00), adjusted to 2014/2015 prices using PSSRU (2015) Section 116.3 p242, The hospital & community health services (HCHS) index
Total weekly cost associated with PPS health states					**£70.70**

Key: BNF, British National Formulary; CT, computerised tomography; GP, general practitioner; HCHS, hospital & community health services; NHS, National Health Service; PSSRU, Personal Social Services research unit.

5.5.4 Adverse reaction unit costs and resource use

As described in Section 5.4, EQ-5D utility data are assumed to accurately capture the disutilities associated with treatment alternatives for previously treated, advanced RCC patients. It is important, however, to account for the different cost implications of treatment-emergent AEs. The Serious Grade III/IV treatment-emergent AEs described in Sections 4.12 and 5.4.3 and their estimated cost are shown in Table 53. A targeted search of the literature revealed scant data on resource use associated with AEs. In TA333, the manufacturer assumed that Grade II/IV diarrhoea would lead to two days hospitalisation and assumed resource use for Grade II/IV anaemia, based on a cost estimate from a study of untreated advanced RCC patients.[109] Meetings with medical oncologists were used to elicit resource use estimates for the Serious Grade III/IV AEs in the model; the detailed descriptions of resource use in Table 53 are informed by these meetings.

Applying these costs to the cycle probability of each event, calculated from CheckMate 025 data and reported in Sections 4.12 and 5.4.3, produces AE cycle costs of £0.35 for nivolumab and £1.31 for everolimus, as shown in Table 54.

In line with assumptions described in the scenario in Section 5.4.3, the cycle cost associated with Serious Grade III/IV AEs for axitinib patients is assumed to be equivalent to AE cycle cost for everolimus patients in Table 48. Given the relative safety profile of nivolumab versus axitinib, the only recommended active treatment for NHS patients with advanced, previously treated RCC (Section 4.12), this approach is conservative.

Table 53: Costs associated with treatment-emergent AEs

Serious Grade III/IV AE	Cost per episode	Source
Pneumonitis	£418.91	Bronchoscopy (19 years and over): £316, regular day and night admissions (DZ69A) NHS reference costs 2014-2015 Weekly OP appointments with a GP: 11.7 minutes of patient contact, excluding direct staff costs and without qualifications £33. Average across both arms is 2.93 weeks = £96.53 per episode (PSSRU 2015) Four weeks of steroids: Fluticasone propionate, 50 microgram per inhalation, 60 inhalations=£6.38 (based on 100mg (i.e. 2 inhalations) per day for 30 days) (MIMS, http://www.mims.co.uk/drugs/respiratory-system/asthma-copd/flixotide-evohaler)
Diarrhoea	£35.83	GP appointment (from PSSRU 2015, excluding direct staff costs, without qualifications, per patient contact lasting 11.7 minutes) £34 Loperamide (dose for acute diarrhoea, 4mg initially, then 2mg after each loose stool; max 16mg daily, from MIMS, assuming the entire prescription is filled) 2mg cap, 30=£1.83
Anaemia	£421.62	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9
Pneumonia	£640.60	Lobar, atypical or viral pneumonia without interventions with CC score 7-9 = £399 (DZ11T), Regular day and night admissions, NHS reference costs 2014-2015 Computerised tomography scan of one area, without contrast, 19 years and over (RD20A), £85, diagnostic imaging. Ampicillin, 500mg powder for solution for injection in vial, 10=£78.30, assuming 500mg four times daily (four administrations per day for 5 days = 20 administrations) £156.60 (MIMS, http://www.mims.co.uk/drugs/infections-and-infestations/bacterial-infections/ampicillin)

Key: AE, adverse event, CC, xxx; GP, general practitioner; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OP, outpatient; PSSRU, Personal Social Services Research Unit.

Table 54: Weekly costs attributable to treatment-emergent AEs

Serious Grade III/IV AE	Nivolumab		Everolimus	
	Cycle probability	Event cost	Cycle probability	Event cost
Pneumonitis	0.001	£418.91	0.001	£418.91
Diarrhoea	0.000	£35.83	0.000	£35.83
Anaemia	0.000	£421.62	0.001	£421.62
Pneumonia	0.000	£640.60	0.001	£640.60
Total AE cycle cost	£0.35		£1.31	
Key: AE, adverse event.				

5.5.5 Miscellaneous unit costs and resource use

Subsequent treatment costs

Second-line patients in CheckMate 025 and in clinical practice may go on to receive subsequent active therapy. It was therefore important to account for the cost associated with subsequent therapy for patients on each arm of the model. Table 55 shows the distribution of subsequent therapies received by patients in both arms of CheckMate 025, for all treatments that were received by >5% of patients on either arm. Bevacizumab is not used in the NHS England; Table 56 shows these data reweighted assuming patients would have otherwise received another of the treatments in Table 55.

Table 55: Subsequent therapies received by >5% of patients in CheckMate 025

	FROM	
TO	**Nivolumab**	**Everolimus**
Axitinib	24.15%	36.25%
Bevacizumab	3.17%	5.35%
Everolimus	25.61%	5.60%
Pazopanib	9.02%	15.57%
Sorafenib	6.34%	9.25%
Sunitinib	6.83%	8.27%
SUM	75.12%	80.29%
Note: Sum totals do not sum to 100%; not all patients progressed to further therapy		

Table 56: Subsequent therapies received by >5% of patients in CheckMate 025, reweighted without bevacizumab

	FROM	
TO	**Nivolumab**	**Everolimus**
Axitinib	25.21%	38.84%
Everolimus	26.74%	6.00%
Pazopanib	9.42%	16.68%
Sorafenib	6.62%	9.91%
Sunitinib	7.13%	8.86%
SUM	75.12%	80.29%
Note: Sum totals do not sum to 100%; not all patients progressed to further therapy		

Table 57 shows weekly treatment costs for pazopanib, sorafenib and sunitinib. In the absence of data on the duration of subsequent therapies from CheckMate 025, an average estimate of 15.87 weeks was sourced from the GOLD trial, which compared dovitinib with sorafenib in a third-line RCC population; the median duration of therapy was calculated as an average between the two treatment arms.[75]

Table 57: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators

Drug	Formulation (mg)	Cost per vial/pack	Vials/ tabs per admin	Vials/ Tabs per pack	Dose	Unit	Treatments per week	Method	Proportions of doses received	Total cost per week	Source
Sorafenib	200	£2,980.00	2.00	112	400	mg	14	Oral	100%	**£745.00**	MIMS [a]
Sunitinib	50	£3,138.80	1.00	28	50	mg	4.7	Oral	100%	**£526.87**	MIMS [b]
Pazopanib	400	£1,121.00	2.00	30	800	mg	14	Oral	100%	**£1,046.27**	MIMS [c]

Key: MIMS, Monthly Index of Medical Specialties; Tabs, Tablets; admin, administration.
Notes: [a] (Antineoplastics - Nexavar) Accessed 20 January 2016; [b] (Antineoplastics - Sutent) Accessed 20 January 2016; [c] (Antineoplastics - Votrient) Accessed 20 January 2016.

To estimate the subsequent therapy costs across treatment arms in the base case analysis, the distribution of subsequent treatments in

Table 56 were multiplied by weekly treatment costs in Table 50 and Table 57. Finally, this figure was multiplied by 15.87 weeks. The resulting treatment costs across each model arm are shown in Table 58. This was applied in the model as a one-off cost upon treatment discontinuation.

In the base case analysis, subsequent treatment costs for axitinib are assumed to be equal to those estimated for everolimus. A scenario in Section 5.8.3 assumes that subsequent treatment costs for nivolumab are also equal to those estimated for everolimus. Patients who receive BSC at second-line are assumed not to go on to have subsequent active therapy.

Table 58: Subsequent therapy costs across model arms

Intervention / Comparator	One-off subsequent treatment cost
Nivolumab	£9,026.29
Everolimus	£10,770.91
Axitinib	£10,770.91
BSC	£0.00
Key: BSC, best supportive care.	

Terminal care costs

The cost of care immediately prior to death is taken from a King's Fund report into improving choice at end of life[110], and is the average cost of community and acute care for patients with cancer in the last eight weeks of their life reported by the authors, inflated to 2014/2015 levels.[123]

The cost for 8 weeks of care is £6,159.66. This is assumed to be spread evenly across the last 8 weeks of a patient's life and is applied as a cost of £769.96 per week to the proportion of patients in the "Terminal care" health state.

Not all of these costs are direct NHS costs – some fall on 'third sector' healthcare organisations; however, their inclusion is relevant to the disease, and does not introduce any bias, as over 99% of patients die within the model time horizon in the base case analysis.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 59: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	See Section
Intervention and comparator treatment costs			
Nivolumab weekly drug costs (100mg formulation)	£878.96	Not included in SA	Section 5.5
Nivolumab weekly drug costs (40mg formulation)	£402.79	Not included in SA	
Everolimus weekly drug costs	£587.77	Not included in SA	
Axitinib weekly drug costs	£896.84	Not included in SA	
Admin and health state costs			
One-off progression costs	£0.00	Not included in SA	Section 5.5
End of life costs	£6,159.66	Gamma (5011.75,7424.18)	
GP visit cost	£37.00	Gamma (30.1,44.6)	
Community Nurse Visit Cost	£65.00	Gamma (52.89,78.34)	
CT Scan cost	£136.00	Gamma (110.66,163.92)	
Blood Test cost	£3.00	Gamma (2.44,3.62)	
Consultant visit cost	£189.00	Gamma (153.78,227.8)	
Disease management analgesic costs	£5.30	Gamma (4.31,6.38)	
Nivolumab administration cost - first visit	£186.53	Gamma (151.77,224.82)	
Nivolumab administration cost - subsequent visits	£186.53	Gamma (151.77,224.82)	
Everolimus administration cost	£0.00	Not included in SA	
Axitinib administration cost	£0.00	Not included in SA	
Adverse event costs			
Pneumonitis event cost	£418.91	Gamma (340.84,504.91)	Section 5.5
Diarrhoea event cost	£35.83	Gamma (29.15,43.19)	
Anaemia event cost	£421.62	Gamma (343.05,508.17)	

Pneumonia event cost	£640.60	Gamma (521.22,772.11)	
Resource use			
Nivolumab drug administration frequency	0.50	Not included in SA	Section 5.5
Everolimus drug administration frequency	0.00	Not included in SA	
Axitinib drug administration frequency	0.00	Not included in SA	
GP visits per week, PFS	0.25	Gamma (0.2,0.3)	
CT scans per week, PFS	0.08	Gamma (0.07,0.1)	
Blood tests per week, PFS	0.25	Gamma (0.2,0.3)	
GP visits per week, PPS	0.25	Gamma (0.2,0.3)	
Community nurse visits per week, PPS	0.38	Gamma (0.31,0.45)	
Pain medication doses per week, PPS	7.00	Gamma (5.7,8.44)	
Health state utilities			
Mixed model parameter, Constant	0.80	Sampling using variance-covariance matrix and random draws from the multivariate-normal distribution	Section 5.4
Mixed model parameter, Decrement - assigned to the comparator arm	-0.04		
Mixed model parameter, Decrement - disease progression	-0.07		
Mixed model parameter, Decrement – interaction; disease progression and assigned to the comparator arm	0.00		
AXIS trial PFS estimate	0.69	Beta (0.66,0.72)	
AXIS trial PPS estimate	0.61	Beta (0.58,0.64)	
Adverse event disutilities			
Pneumonitis event disutility	-0.15	Beta (-0.12,-0.18)	Section 5.4
Diarrhoea event disutility	-0.10	Beta (-0.08,-0.12)	
Anaemia event disutility	-0.08	Beta (-0.07,-0.1)	
Pneumonia event disutility	-0.13	Beta (-0.11,-0.16)	
Adverse event probabilities			
Pneumonitis probability nivolumab	0.00	Beta (0,0)	Section 5.4
Diarrhoea probability nivolumab	0.00	Beta (0,0)	
Anaemia probability nivolumab	0.00	Beta (0,0)	
Pneumonia probability nivolumab	0.00	Beta (0,0)	

Pneumonitis probability everolimus	0.00	Beta (0,0.01)	
Diarrhoea probability everolimus	0.00	Beta (0,0)	
Anaemia probability everolimus	0.00	Beta (0,0)	
Pneumonia probability everolimus	0.00	Beta (0,0)	
Survival parameters			
OS Dependent, Generalised Gamma, mu	3.16	Sampling using variance-covariance matrix and random draws from the multivariate-normal distribution	Section 5.3
OS Dependent, Generalised Gamma, sigma	1.08		
OS Dependent, Generalised Gamma, Q	0.51		
OS Dependent, Generalised Gamma, Trt	0.29		
HR crossover, nivolumab versus placebo, OS	0.60	Sampling from parameter uncertainty using random draws	
HR crossover, nivolumab versus axitinib, OS	0.84		
PFS Independent Nivo, Spline 2 knots odds, gamma 0	-0.71	Sampling using variance-covariance matrix and random draws from the multivariate-normal distribution	
PFS Independent Nivo, Spline 2 knots odds, gamma 1	6.17		
PFS Independent Nivo, Spline 2 knots odds, gamma 2	0.51		
PFS Independent Nivo, Spline 2 knots odds, gamma 3	-0.41		
PFS Independent Ever, Spline 2 knots odds, gamma 0	-1.03	Sampling using variance-covariance matrix and random draws from the multivariate-normal distribution	
PFS Independent Ever, Spline 2 knots odds, gamma 1	5.04		
PFS Independent Ever, Spline 2 knots odds, gamma 2	0.49		
PFS Independent Ever, Spline 2 knots odds, gamma 3	-0.48		
HR ITT, nivolumab versus placebo, PFS	0.33	Sampling from parameter uncertainty using random draws	
HR ITT, nivolumab versus axitinib, PFS	0.87		
TTD Dependent, Spline 2 knots hazard, gamma 0	-2.41	Sampling using variance-covariance matrix and random draws from the multivariate-normal distribution	
TTD Dependent, Spline 2 knots hazard, gamma 1	3.15		
TTD Dependent, Spline 2 knots hazard, gamma 2	0.30		
TTD Dependent, Spline 2 knots hazard, gamma 3	-0.27		
TTD Dependent, Spline 2 knots hazard, Trt	-0.68		

Key: CI, confidence interval; CT, computerised tomography; GP, general practitioner; HR, hazard ration; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; SA, survival analysis; TTD, time to treatment discontinuation.

5.6.2 Assumptions

The base case analysis is subject to several key assumptions, described and discussed throughout Section 5. For reference, these key assumptions are summarised here. Uncertainties regarding each of these assumptions are explored in Section 5.8.

Effectiveness

1. OS for nivolumab and everolimus is best characterised by generalised gamma curves fitted to CheckMate 025 data, un-stratified by treatment arm
2. PFS for nivolumab and everolimus is best characterised by a spline odds model with two intermediate knots fitted to CheckMate 025 data, stratified by treatment arm
3. Crossover-adjusted HRs from the NMA of OS data across trials, reported in Section 4.10, are appropriate to estimate OS for axitinib and BSC
4. ITT HRs from the NMA of PFS data across trials, reported in Section 4.10, are appropriate to estimate PFS for axitinib and BSC

Quality of life

1. Quality of life is dependent on treatment received and progression status
2. The most suitable sources to estimate utilities are CheckMate 025 EQ-5D data for nivolumab and everolimus patients, and AXIS EQ-5D data from axitinib patients for axitinib and BSC

Resource use and costs

1. Treatment duration for nivolumab and everolimus patients is best characterised by a spline hazard model with two intermediate knots fitted to CheckMate 025 TTD data, stratified by treatment arm
2. Vial sharing will not occur in practice in the administration of nivolumab
3. Axitinib patients are treated to progression
4. BSC is associated with no active treatment costs

5. Disease management resource use is dependent on RECIST-defined progression status

3. NHS costs of treatment-related AEs are captured by medical oncologists' estimates of resource use associated with Serious Grade III/IV AEs

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Table 60 shows base case results and pairwise analyses of incremental results. While BMS are aware that axitinib has been recommended on the basis of a confidential discount, all results are presented using list prices.

Nivolumab is shown to be a highly effective therapy, versus axitinib, everolimus and BSC, with a predicted survival benefit of 1.35 years (1.07 QALYs) versus axitinib, 0.89 years (0.63 QALYs) versus everolimus and 1.97 years (1.43 QALYs) versus BSC. For patients currently receiving axitinib, the only recommended active treatment for previously treated, advanced RCC, results suggest nivolumab is a cost-effective end-of-life alternative for the NHS.

Table 60: Base-case results; pairwise analysis, nivolumab versus comparator

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£46,133.83	1.25	2.09	£45,218.83	1.07	1.35	£42,417.26
Everolimus	£38,920.38	1.69	2.55	£52,432.28	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,827.72	1.43	1.97	£56,427.43
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

5.7.2 Clinical outcomes from the model

Table 61 shows predicted median OS and PFS, from extrapolations informing the economic analysis. Table 62 shows observed median OS and PFS from key trials used in the economic analysis.

Comparison of data in these tables suggests the model predicts median OS and PFS for nivolumab and everolimus accurately, as described in Section 5.3.

Model predictions of median OS and PFS for axitinib are lower than those reported for all patients randomised to axitinib in the AXIS trial, but considering analyses of the subgroup of patients who had received prior sunitinib[99], the base case model over-predicts OS for axitinib. When ITT NMA results are used, the model predicts median OS for axitinib to be similar to that observed across all patients in the axitinib arm of the AXIS study.[99]

For BSC (placebo), the base case model accurately predicts PFS, but over-predicts OS in comparison to the RPSFT-adjusted median OS estimate from the RECORD-1 trial. This over-prediction is even greater when ITT NMA results are used to inform the economic model.

Table 61: Modelled median OS and PFS, months

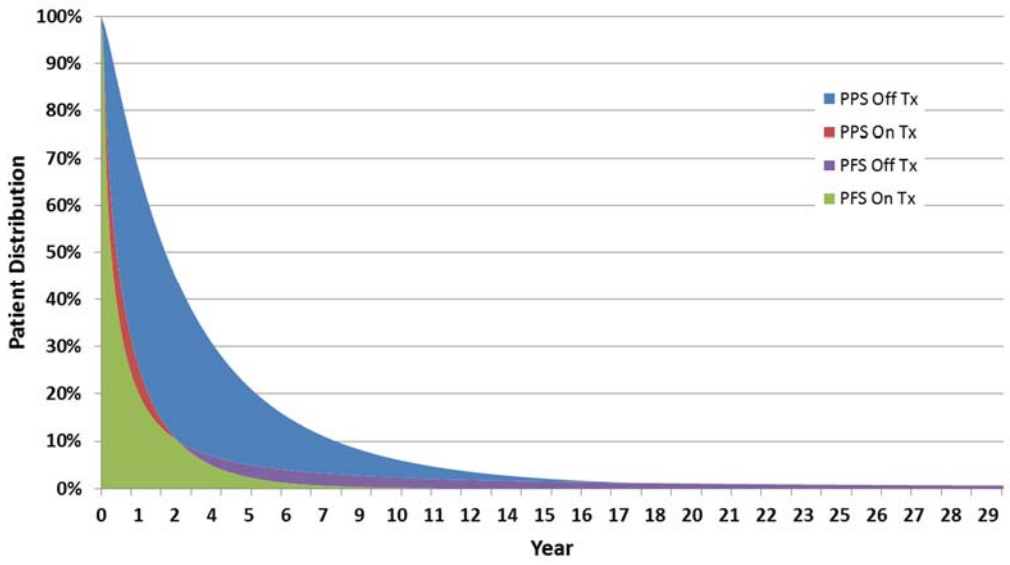
Outcome	Nivolumab	Axitinib		Everolimus	BSC	
		Crossover NMA	ITT NMA		Crossover NMA	ITT NMA
Median PFS	4.4	3.9	3.9	4.6	1.8	1.8
Median OS	26.0	16.6	19.5	19.5	17.2	12.2
Key: BSC, best supportive care; PFS, progression-free survival; OS, overall survival						

Table 62: Key trial estimates of median OS and PFS, months

Outcome	Treatment and Study					
	Nivolumab	Axitinib		Everolimus		BSC
	CheckMate 025	AXIS	AXIS*	CheckMate 025	Record-1	RECORD-1**
Median PFS	4.6	6.7	4.8	4.7	4.9	1.9
Median OS	25.0	20.1	15.2	19.6	14.8	10.0
Key: BSC, best supportive care; PFS, progression-free survival; OS, overall survival **Notes:*** subgroup previously treated with sunitinib; ** RPSFT adjusted median OS						

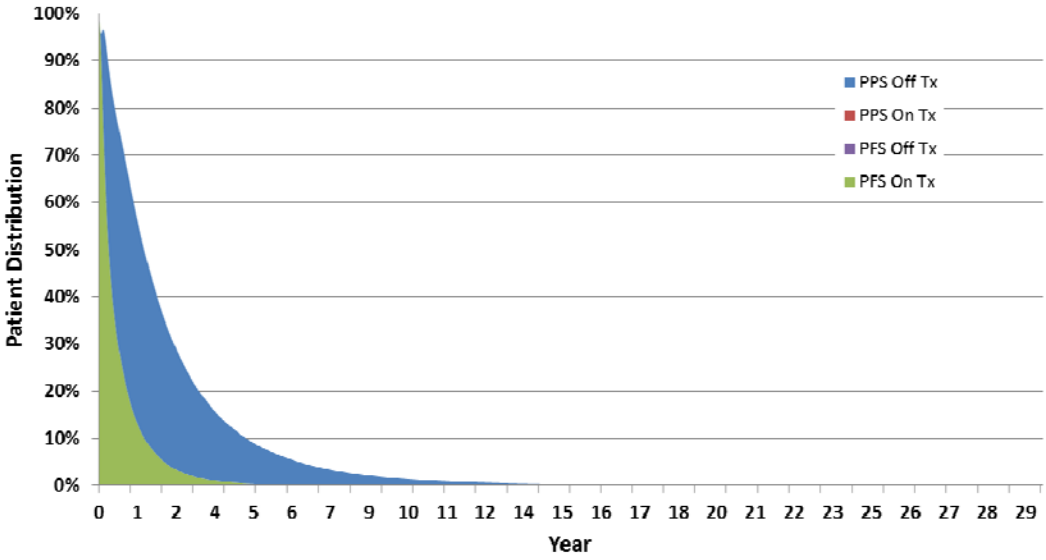
Figure 46 to Figure 48 depict Markov traces for nivolumab and the three comparator treatments. Even without immuno-response OS and PFS tails expected by the clinical community, given the mechanism of nivolumab and evidence from melanoma patients, nivolumab offers a visible pre- and post-progression survival benefit to previously treated RCC patients.

Figure 46: Markov trace, nivolumab



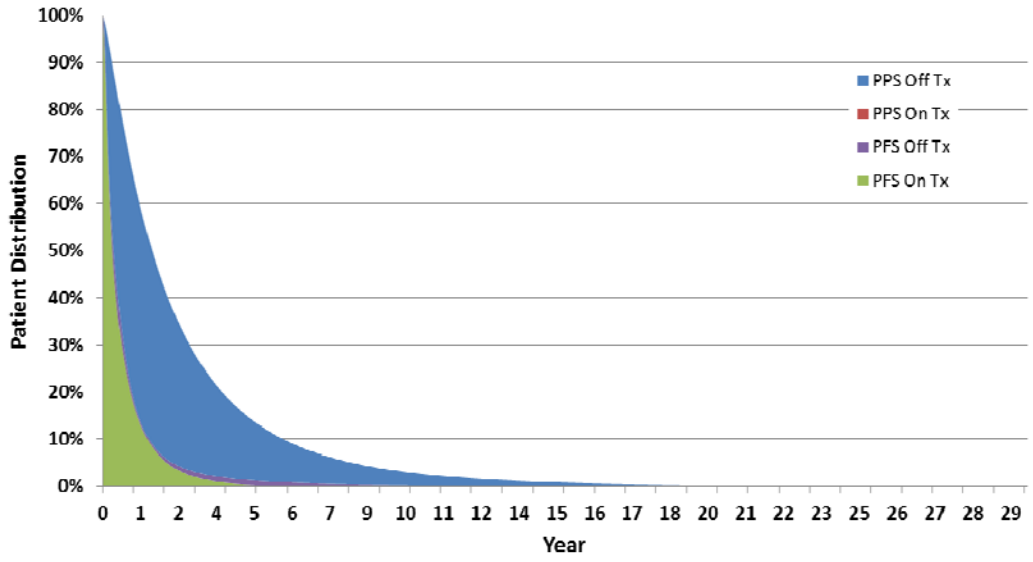
Key: PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

Figure 47: Markov trace, axitinib



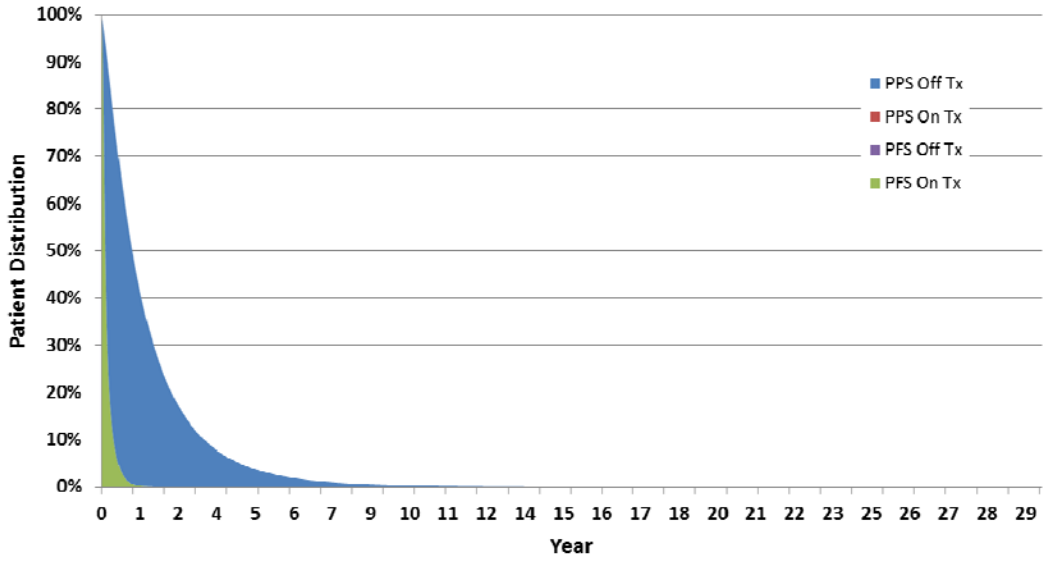
Key: PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

Figure 48: Markov trace, everolimus



Key: PFS, progression-free survival; PPS, post-progression survival; Tx, treatment

Figure 49: Markov trace, BSC



Key: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 63, Table 64 and Table 65 summarise total QALYs for each arm of the base case model, disaggregated by model health states. Reflecting Figure 46 to Figure 49, nivolumab is predicted to offer a health benefit across model health states and versus each comparator. These findings are consistent with the immune-response mechanism of nivolumab, and treatment beyond progression of many nivolumab patients.

Table 63: Summary of QALY gain by health state, nivolumab versus axitinib

Health State	Nivolumab	Axitinib	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	0.69	0.39	0.29	0.29	27%
PFS Off Treatment	0.22	0.00	0.22	0.22	20%
PPS On Treatment	0.10	0.00	0.10	0.10	9%
PPS Off Treatment	1.31	0.85	0.46	0.46	43%
Total	2.31	1.25	1.07	1.07	100%
Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Table 64: Summary of QALY gain by health state, nivolumab versus everolimus

Health State	Nivolumab	Everolimus	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	0.69	0.45	0.23	0.23	38%
PFS Off Treatment	0.22	0.07	0.14	0.14	23%
PPS On Treatment	0.10	0.00	0.10	0.10	15%
PPS Off Treatment	1.31	1.16	0.15	0.15	24%
Total	2.31	1.69	0.63	0.63	100%
Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Table 65: Summary of QALY gain by health state, nivolumab versus BSC

Health State	Nivolumab	BSC	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	0.69	0.14	0.55	0.55	38%
PFS Off Treatment	0.22	0.00	0.22	0.22	15%
PPS On Treatment	0.10	0.00	0.10	0.10	7%
PPS Off Treatment	1.31	0.74	0.57	0.57	40%
Total	2.31	0.88	1.43	1.43	100%
Key: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Table 66, Table 67 and Table 68 show predicted total incremental costs for nivolumab versus each of the three base case comparators, across health states. Table 69, Table 70 and Table 71 show these data further aggregated by different resource use categories.

Table 66: Summary of costs by health state, nivolumab versus axitinib

Health State	Nivolumab	Axitinib	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	£62,779	£27,326	£35,453	£35,453	72%
PFS Off Treatment	£301	£0	£301	£301	1%
PPS On Treatment	£9,944	£0	£9,944	£9,944	20%
PPS Off Treatment	£6,658	£5,157	£1,501	£1,501	3%
Terminal Care	£5,541	£5,727	-£186	£186	0%
One-off costs	£6,129	£7,924	-£1,795	£1,795	4%
Total	£91,353	£46,134	£45,219	£45,219	100%
Key: PFS, progression-free survival; PPS, post-progression survival.					

Table 67: Summary of costs by health state, nivolumab versus everolimus

Health State	Nivolumab	Everolimus	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	£62,779	£18,871	£43,908	£43,908	77%
PFS Off Treatment	£301	£106	£196	£196	0%
PPS On Treatment	£9,944	£0	£9,944	£9,944	18%
PPS Off Treatment	£6,658	£6,155	£503	£503	1%
Terminal Care	£5,541	£5,667	-£126	£126	0%
One-off costs	£6,129	£8,122	-£1,992	£1,992	4%
Total	£91,353	£38,920	£52,432	£52,432	100%
Key: PFS, progression-free survival; PPS, post-progression survival.					

Table 68: Summary of costs by health state, nivolumab versus BSC

Health State	Nivolumab	BSC	Increment	Absolute Increment	% Absolute Increment
PFS On Treatment	£62,779	£233	£62,546	£62,546	77%
PFS Off Treatment	£301	£0	£301	£301	0%
PPS On Treatment	£9,944	£0	£9,944	£9,944	12%
PPS Off Treatment	£6,658	£4,500	£2,158	£2,158	3%
Terminal Care	£5,541	£5,792	-£251	£251	0%
One-off costs	£6,129	£0	£6,129	£6,129	8%
Total	£91,353	£10,525	£80,828	£80,828	100%
Key: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival.					

Table 69: Summary of predicted resource use by health state and cost category, nivolumab versus axitinib

Health State and Cost Category	Nivolumab	Axitinib	Increment	Absolute Increment	% Absolute Increment
PFS on Tx, Treatment Acquisition Costs	£57,612	£26,653	£30,959	£30,959	63%
PFS on Tx, Treatment Administration Costs	£4,192	£0	£4,192	£4,192	9%
PFS on Tx, Adverse Event Costs	£16	£39	-£23	£23	0%
PFS on Tx, Disease Management Costs	£959	£634	£325	£325	1%
PFS, off Tx, Disease Management Costs	£301	£0	£301	£301	1%
One-off progression costs	£0	£0	£0	£0	0%
Subsequent therapy cost	£6,129	£7,924	-£1,795	£1,795	4%
PPS, on Tx, Treatment Acquisition Costs	£8,814	£0	£8,814	£8,814	18%
PPS, on Tx, Treatment Administration Costs	£641	£0	£641	£641	1%
PPS, on Tx, Adverse Event Costs	£2	£0	£2	£2	0%
PPS, on Tx, Disease Management Costs	£486	£0	£486	£486	1%
PPS, off Tx, Disease Management Costs	£6,658	£5,157	£1,501	£1,501	3%
EOL Cost	£5,541	£5,727	-£186	£186	0%
Total	£91,353	£46,134	£45,219	£45,219	100%
Key: EOL, end of life; PFS, progression-free survival; PPS, post-progression survival; Tx					

Table 70: Summary of predicted resource use by health state and cost category, nivolumab versus everolimus

Health State and Cost Category	Nivolumab	Everolimus	Increment	Absolute Increment	% Absolute Increment
PFS on Tx, Treatment Acquisition Costs	£57,612	£18,210	£39,402	£39,402	70%
PFS on Tx, Treatment Administration Costs	£4,192	£0	£4,192	£4,192	7%
PFS on Tx, Adverse Event Costs	£16	£0	£16	£16	0%
PFS on Tx, Disease Management Costs	£959	£661	£298	£298	1%
PFS, off Tx, Disease Management Costs	£301	£106	£196	£196	0%
One-off progression costs	£0	£0	£0	£0	0%
Subsequent therapy cost	£6,129	£8,122	-£1,992	£1,992	4%
PPS, on Tx, Treatment Acquisition Costs	£8,814	£0	£8,814	£8,814	16%
PPS, on Tx, Treatment Administration Costs	£641	£0	£641	£641	1%
PPS, on Tx, Adverse Event Costs	£2	£0	£2	£2	0%
PPS, on Tx, Disease Management Costs	£486	£0	£486	£486	1%
PPS, off Tx, Disease Management Costs	£6,658	£6,155	£503	£503	1%
EOL Cost	£5,541	£5,667	-£126	£126	0%
Total	£91,353	£38,920	£52,432	£52,432	100%
Key: EOL, end of life; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.					

Table 71: Summary of predicted resource use by health state and cost category, nivolumab versus BSC

Health State and Cost Category	Nivolumab	BSC	Increment	Absolute Increment	% Absolute Increment
PFS on Tx, Treatment Acquisition Costs	£57,612	£0	£57,612	£57,612	71%
PFS on Tx, Treatment Administration Costs	£4,192	£0	£4,192	£4,192	5%
PFS on Tx, Adverse Event Costs	£16	£13	£2	£2	0%
PFS on Tx, Disease Management Costs	£959	£219	£739	£739	1%
PFS, off Tx, Disease Management Costs	£301	£0	£301	£301	0%
One-off progression costs	£0	£0	£0	£0	0%
Subsequent therapy cost	£6,129	£0	£6,129	£6,129	8%
PPS, on Tx, Treatment Acquisition Costs	£8,814	£0	£8,814	£8,814	11%
PPS, on Tx, Treatment Administration Costs	£641	£0	£641	£641	1%
PPS, on Tx, Adverse Event Costs	£2	£0	£2	£2	0%
PPS, on Tx, Disease Management Costs	£486	£0	£486	£486	1%
PPS, off Tx, Disease Management Costs	£6,658	£4,500	£2,158	£2,158	3%
EOL Cost	£5,541	£5,792	-£251	£251	0%
Total	£91,353	£10,525	£80,828	£80,828	100%

Key: BSC, best supportive care; EOL, end of life; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

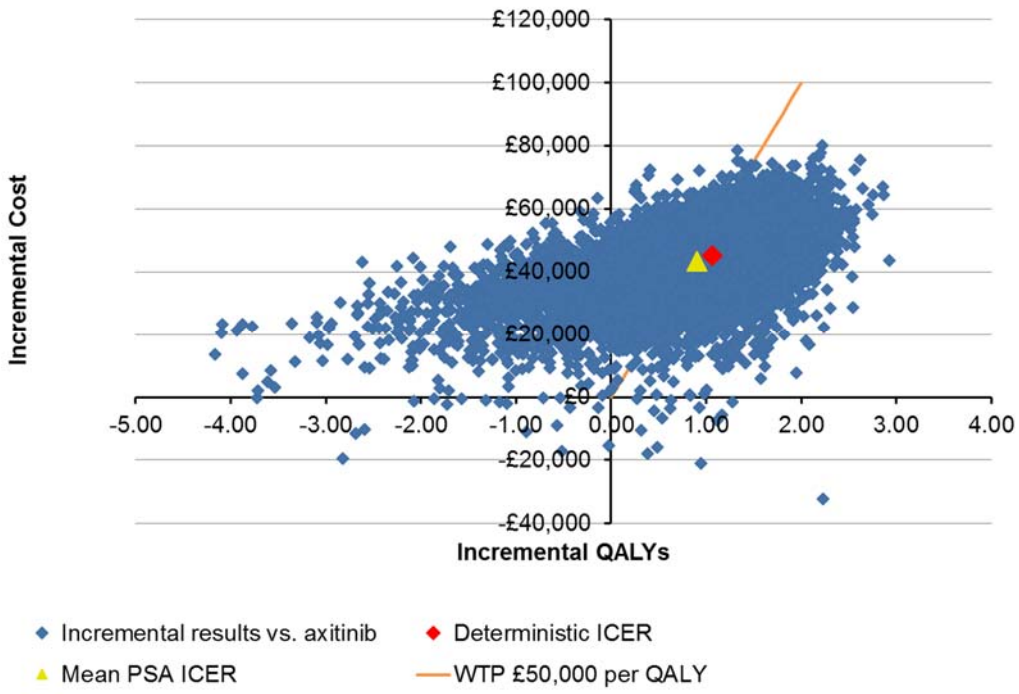
5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Figure 50 shows a PSA scatterplot for the key comparison of nivolumab versus axitinib. Ten thousand PSA iterations were run; a sufficient number for the point estimate of the HR for OS, everolimus versus axitinib, to stabilise. Table 72 shows mean probabilistic base case results. PSA scatterplot diagrams for comparisons to everolimus and BSC are presented in Appendix 8.

Scatterplots show that there is some parameter uncertainty around the mean ICER. The majority of the uncertainty comes from the variability of QALY estimates due to the uncertainty in survival curve predictions and in particular, the crossover-adjusted HR for OS, everolimus versus axitinib. Despite the skew of PSA estimates, the results suggest nivolumab is a cost-effective alternative to axitinib at a willingness-to-pay threshold of £50,000 per QALY gained (probability=0.608). Importantly, and as demonstrated in Section 5.6, the scale of uncertainty around parameter estimates was informed by data and not arbitrary assumptions for key parameters, including all survival parameters and health state utility parameters. Every effort has been made to ensure the parameter uncertainty shown in scatterplots is reflective of true parameter uncertainty.

Figure 50: PSA scatterplot, nivolumab versus axitinib



Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Table 72: Mean probabilistic base case results, pairwise comparisons

	Total costs	QALYs	Life Years	Incremental, Nivolumab versus comparator			ICER
				Costs	QALYs	Life Years	
Nivolumab	£91,964	2.36	3.55				
Axitinib	£48,655	1.46	2.59	£43,310	0.90	0.96	£47,928
Everolimus	£39,127	1.72	2.62	£52,838	0.64	0.93	£82,288
BSC	£11,270	1.02	1.77	£80,694	1.34	1.78	£60,077

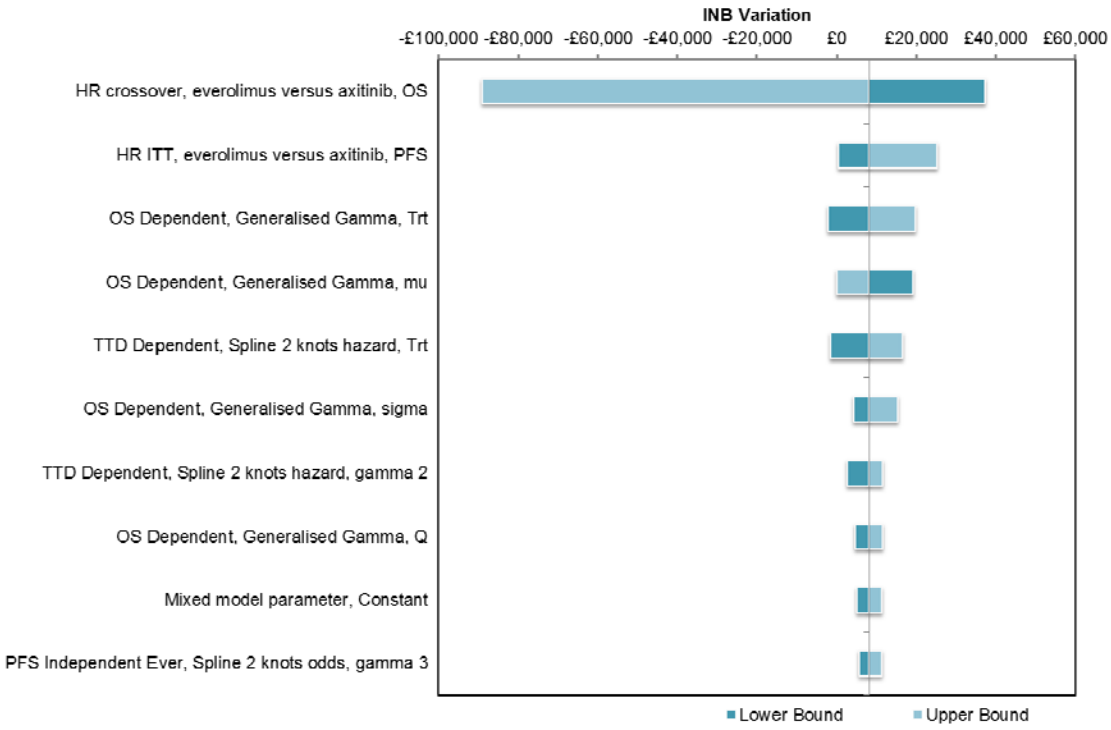
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.8.2 Deterministic sensitivity analysis

Figure 51 shows a tornado diagram depicting the ten parameters with the greatest influence upon the estimate of incremental net benefit in the one-way sensitivity analysis (OWSA), and the influence they had upon results when varied to upper and lower 95% CI values, for the key comparison to axitinib. The analyses assume a willingness-to-pay threshold of £50,000 per QALY gained. Tornado diagrams for comparisons to everolimus and BSC are presented in Appendix 8.

Results are robust to isolated parameter changes to the vast majority of variables in the model. In line with PSA results, uncertainty around survival curve parameter estimates are shown to have the greatest influence on results, and the uncertainty around crossover-adjusted NMA results for OS is shown to be particularly important. As described in Section 5.6 and above, the scale of uncertainty around these parameter estimates was informed by robust data and not arbitrary assumptions.

Figure 51: Tornado diagram showing OWSA results, nivolumab versus axitinib



Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation.

5.8.3 Scenario analysis

Table 73 shows results from scenario analyses varying key assumptions in the base case key comparison to axitinib. Results are robust to changes in assumptions surrounding time horizon, the health consequences of AEs, disease management resource use, subsequent treatment cost assumptions, and structural uncertainty regarding parametric extrapolation of CheckMate 0325 OS data.

Assuming, in the absence of robust evidence from CheckMate 025 but in line with immune-therapy evidence elsewhere, that nivolumab patients who survive for five years then have a similar mortality risk to the age-matched general population, dramatically reduced the key ICER versus axitinib, to less than £23,000 per QALY gained.

Assuming average patient weight of 72.45kg, from IPSOS market research, instead of 80.93kg, from Western European patients in CheckMate 025, led to a substantial

fall in the estimated key ICER, relative to the base case, from £42,417 to less than £36,150. Costing to match clinical expectations of vial sharing also reduced the key ICER estimate considerably, to less than £39,950.

There is some sensitivity to annual discount rate assumptions, which is likely driven by the predicted long-term benefit associated with treatment with nivolumab. Adopting alternative utility assumptions for axitinib caused the estimated key ICER to increase, but remain below a willingness to pay threshold of £50,000 per QALY gained. Using the OS HR from the ITT NMA described in Section 4.10 increases the key ICER estimate to less than £51,750.

Table 73: Scenario analysis results

Parameter	Base case	Scenario analysis	Nivolumab vs Axitinib ICER
BASE CASE			**£42,417**
Discount rate (costs and utilities)	3.5%	6%	£45,407
Discount rate (costs and utilities)	3.5%	0%	£37,598
Time horizon	30 years	20 years	£43,577
Time horizon	30 years	25 years	£42,879
Time horizon	30 years	35 years	£42,100
OS NMA analysis choice	Crossover-adjusted	ITT	£51,728
OS curve choice	Generalised Gamma	Exponential	£44,069
Vial sharing	No	Yes	£39,947
Nivolumab survival benefit	No immuno-response effect	Include immuno-response effect	£22,923
Health state resource use	TA 333 assumptions	Clinician estimates	£41,617
Subsequent treatment costs for nivolumab	As per CHECKMATE-025	Equal to everolimus	£43,529
Axitinib utility source	AXIS patients	TA 333 historical estimates	£48,811
Axitinib utility source	AXIS patients	025 Trial everolimus patients	£49,982
AE utility decrements	Exclude	Include	£42,414
Average patient weight	025 Western European patients	IPSOS UK estimate	£36,149

Key: AE, adverse event; BSC, best supportive care; ITT, intention to treat; NMA, network meta-analysis; OS, overall survival, TA, Technology Appraisal

5.8.4 Summary of sensitivity analyses results

Probabilistic and one-way sensitivity analysis results showed results to be robust to changes in the majority of model parameters. Uncertainty around ICERs was largely driven by uncertainty around NMA HR estimates, and to a lesser extent, uncertainty around parametric curve fits to CheckMate 025 survival data. Projections of clinical outcomes from CheckMate 025 data and using NMA results have been validated at clinical review, following NICE DSU guidance, in an effort to be transparent and accurate in our clinical assumptions.

Base case results were shown to be robust to further parameter and methodological assumptions explored in scenario analyses, in which the cost-effectiveness of nivolumab was shown to be robust to assumptions surrounding time horizon, the costs and health consequences of AEs, disease management resource use, subsequent treatment cost assumptions, and structural uncertainty around OS modelling. There is some sensitivity to discount rate assumptions, the approach to the NMA, and utility assumptions for axitinib patients, while adopting alternative but plausible assumptions about patient weight and vial sharing reduce the key ICER estimate substantially. If, in line with clinical expectations, there is an immune-response survival effect for a proportion of patients treated with nivolumab, the base case analysis may be dramatically underestimating the cost-effectiveness of nivolumab.

5.9 Subgroup analysis

Subgroup analyses of clinical outcomes in Section 4.8 showed the estimated OS and ORR benefit of nivolumab versus everolimus from Checkmate 025 data to be consistent across subgroups defined by PD L1 tumour expression status, MSKCC score, IMDC risk score, number of sites and types of metastases, number and types of prior therapies received, and duration of first-line treatment. Further subgroup analysis was not explored in the economic model.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The economic approach was designed to be consistent with previous appraisals of innovative treatments for patients with previously treated, advanced RCC, and to be sufficiently flexible to capture the key clinical outcomes affecting NHS/PSS costs and patient HRQL, as described in Section 5.2.

Meetings with oncologists, each currently treating patients with advanced RCC within the NHS in England or Wales and each with some experience of HTA, were a crucial step in validating and informing key analysis assumptions. Separate meetings were held with: Professor John Wagstaff, Deputy Clinical Director, South West Wales Cancer Research Institute, Swansea; Dr James Larkin, Consultant Medical Oncologist, The Royal Marsden NHS Foundation Trust; and a third medical oncologist who preferred not to be named in this submission. Each has experience of treating RCC patients with nivolumab from clinical trials, and of currently available treatments, from NHS practice.

Each meeting comprised a 60-90 minute discussion, covering five pre-defined topics: the suitability of the proposed model to capture key outcomes; validation of survival extrapolations; the patient HRQL experience and validity of utility estimates; validation of resource use estimates from TA333; resources and patient HRQL associated with key adverse events. Notes from each of those meetings are disclosed as part of this submission [102].

The model was quality-assured by the internal processes of the external economists who adapted the economic model. In these processes, an economist not involved in model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions.

5.11 Interpretation and conclusions of economic evidence

As described in Section 5.10, the methods and data used to analyse the cost-effectiveness of nivolumab for previously treated, advanced RCC patients have been validated and are believed to be the best available. The clarity, transparency and usefulness of the evidence presented are the main strengths of the economic evaluation. The main weakness of the evaluation is the immaturity and power of the key OS data, which are not sufficient to demonstrate an immune-response OS tail, expected by the clinical community based on mechanism of action and evidence for nivolumab in melanoma patients. That it was not possible to systematically review the economic, cost and utility literature in time for this submission is another weakness, but considered mitigated by the recent history of appraisal evidence in this indication, and the availability of patient-reported EQ-5D data from CheckMate 025.

Analysis of results has shown estimates of overall and progression-free survival and of relative treatment effectiveness from NMA results, to be key model drivers. The methods used to analyse survival data from CheckMate 025 and synthesise data across studies have followed NICE DSU methods guidance documents [124], including validation of results at clinical review. It is difficult to validate projections of survival for patients who received nivolumab in CheckMate 025, given the limited additional evidence for nivolumab in previously treated, advanced RCC patients. Section 5.7.2 compared median overall and progression-free survival estimates from the economic analysis to corresponding estimates from key trials. The base case and sensitivity and scenario analyses presented are sufficient to make a conservative comparison between nivolumab and axitinib, and versus everolimus and BSC.

Overall, the economic analysis suggests that nivolumab is a cost-effective treatment option for the NHS, for previously treated RCC patients who are currently treated with axitinib.

6 Assessment of factors relevant to the NHS and other parties

The total number of patients eligible for treatment for budget impact calculations were calculated as described in Section 3.3.

In 2013, the incidence of kidney cancer in England was 8,505.[54] Through 2005 to 2013, the average annual increase in kidney cancer incidence was approximately 6%.[54] (Office for National Statistics, 2015). Applying the same annual incidence rate for the following 3 years, the predicted incidence of kidney cancer in England for 2016 is 10,130. Assuming that 80% of all cases of kidney cancer are RCC[15, 16] and that 30% of all cases of RCC are advanced at diagnosis [18, 56-59], the predicted incidence of advanced RCC in England for 2016 is 2,431.

From two advisory boards for RCC held by BMS in June 2014 and January 2016[45, 60], it was estimated that 75% of advanced RCC patients will receive systemic therapy at first-line, giving an estimated 1,823 advanced RCC patients who have received at least one prior therapy in 2016. It should be acknowledged that this estimate should be treated with caution as it does not incorporate prevalence data or accommodate for death within the first year of diagnosis (despite active treatment). This is due to the fact that prevalence data and up to date 1-year survival estimates reflecting current practice are not available and therefore cannot be applied.

Severity of disease or concerns over general health (see Section 3.2; 3.5) can also result in patients not receiving subsequent therapy. In current clinical practice, UK experts suggest that approximately half of patients receiving first-line systemic therapy actually go on to receive second-line treatment, giving a total number of patients receiving second-line treatment of 912.[12, 60] A summary of the total eligible patients for each year of the budget impact model is given in Table 74.

Table 74: Total patients starting treatment in budget impact model

	2016	2017	2018	2019	2020
Total number of patients starting treatment	912	967	1021	1076	1131

The acquisition cost and administration cost of treatment were added together to give the total treatment cost for patients in each of these patient groups. Unit costs have been sourced from MIMS online and NHS Reference Costs 2014-2015 and are described in more detail in Section 5.5.

The split of therapies received by each patient is taken from BMS market share analysis and is given in Table 75. If nivolumab becomes available, it is anticipated [redacted] of eligible patients will be treated with nivolumab in year 1. This is predicted to increase to [redacted] in year 2, followed by [redacted] in year 3, and [redacted] in years 4 and 5. The market share for 'Other' treatment was redistributed amongst other treatments proportional to the size of their market share. The market share estimates for nivolumab becoming available show BSC use decreasing marginally over time. This is based on the assumption that that a small percentage of patients not receiving second-line treatment in current practice may be eligible for nivolumab treatment (if recommended for use) in consideration of its favourable safety profile compared to current treatments.

Table 75: Market share estimates

Market share estimates of current care					
	Y1 (2016)	**Y2 (2017)**	**Y3 (2018)**	**Y4 (2019)**	**Y5 (2020)**
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Market share estimates if nivolumab becomes available					
	Y1 (2016)	**Y2 (2017)**	**Y3 (2018)**	**Y4 (2019)**	**Y5 (2020)**
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**99%**	**100%**	**100%**	**100%**	**99%**
Note: Due to rounding, estimates may not sum to 100%					

Patient numbers for budget impact calculations are taken by multiplying eligible patients by survival calculations for each treatment used in the model.

Table 76 shows the expected net budget impact of nivolumab at list price. In year 1 the budget impact is expected to be [redacted] rising to [redacted] in year 5 due to increased uptake.

Table 76: Estimated net budget impact

	Year				
	2016	**2017**	**2018**	**2019**	**2020**
Total number of patients starting treatment	912	967	1021	1076	1131
Patients expected to receive nivolumab	114	316	497	620	694
Cost for total population without nivolumab available	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost for total population of nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost for total population of other treatments when nivolumab is available	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost for total population with nivolumab available	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7 References

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8 Appendices

The following appendices are included in a separate appendices document:

Appendix 1: SmPC and EPAR (Section 2.2)

Appendix 2: Search strategies used to identify relevant RCTs (Section 4.1)

Appendix 3: Secondary data sources for RCTs included in the final evidence base (Section 4.1)

Appendix 4: Quality assessment of nivolumab trials (Section 4.6 & Section 4.11)

Appendix 5: Details of RCTs included in the final evidence base utilised for ITC (Section 4.10)

Appendix 6: Descriptive summary of EQ-5D data (Section 4.7)

Appendix 7: Mixed treatment comparison results for overall survival, HRs for everolimus versus each alternative (Section 4.10)

Appendix 8: Additional economic analysis sensitivity analysis results

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

Dear [redacted],

The Evidence Review Group, BMJ Evidence, and the technical team at NICE have looked at the submission received on 2 March from Bristol Myers Squibb. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **6 April**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues or procedural questions raised in this letter, please contact Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Dr Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

A1. **Priority question**
Please provide the Clinical Study Reports for CheckMate 025, CheckMate 010 and CheckMate 003.

A2. Please provide information of any recent updates to the literature search originally performed in November 2014.

A3. Please clarify whether in CheckMate 025, disease assessment was done independently and if so please provide the data.

A4. Using the table below, please provide the baseline characteristics of UK patients in CheckMate 025.

Characteristics	**Nivolumab (n=)**	**Everolimus (n=)**
Age, median (range), years		
Gender, male n (%)		
Race, n (%) White Asian Black Other		
MSKCC risk group, n (%) Favourable Intermediate Poor		
Karnofsky PS, n (%) <70 70 80 90 100		
Previous nephrectomy, n (%) Yes No		

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Characteristics	Nivolumab (n=)	Everolimus (n=)
Median (range) time from initial diagnosis to randomisation, months		
Previous antiangiogenic regimens for treatment of advanced RCC, n (%) 1 2		
Previous systemic therapy for metastatic RCC, n (%) Sunitinib Pazopanib Axitinib		
PD-L1 expression level, n (%) ≥1% <1% ≥5% <5%		

A5. Please clarify why quality of life was assessed with FKSIDRS rather than FKSI-15, given FKSIDRS is a subscale of FKSI-15.

A6. Please clarify why a full systematic review for non-RCT evidence was not considered necessary.

A7. For each of the trials included in the network, please state which treatments patients had received before entering the trial, including the proportion (number and percent) of patients who had each of these treatments. Please provide this information in the table below.

Trial	Prior treatment(s)	
e.g. CheckMate 025	**Nivolumab:** Sunitinib, n (%) …	**Everolimus:** Sunitinib, n (%) …
CheckMate 025		

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Trial	Prior treatment(s)	
AXIS		
GOLD		
INTORSECT		
RECORD-A		
RECORD-3		
TARGET		
TIVO-1		
VEG105192		
Yang et al 2003		

A8. Please provide the Kaplan Meier curves and estimates of progression-free survival and overall survival from CheckMate 025 (as mean and median times, including standard deviation and confidence intervals) for nivolumab and everolimus (separately) based on previous treatment with a tyrosine kinase inhibitor or cytokine (i.e. 4 Kaplan Meier curves for progression-free survival and 4 Kaplan Meier curves for overall survival in total).

Section B: Clarification on cost-effectiveness data

B1. **Priority question**
Please clarify how events are defined in the time to discontinuation (TTD) survival analysis, and in particular, clarify if patients who die are considered to discontinue treatment or are censored.

B2. **Priority question**
Please clarify the clinical reason why the utility scores for patients in the post-progression health state would be different based on the treatment received (that is, nivolumab or everolimus).

B3. **Priority question**
Please provide further justification for assuming that patients treated with axitinib would have a HRQoL utility score lower than patients who receive nivolumab or everolimus, irrespective of their disease progression status.

B4. **Priority question**

a. Please clarify why treatment status (i.e. on treatment or off treatment) was not taken into account in the mixed model for the CheckMate 025 EQ-5D data analysis.

b. Please test the interactions between the variables and fit of a model including:

i. treatment allocation (nivolumab or everolimus),

ii. disease progression status (not progressed or progressed),

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iii. treatment status (on treatment and off treatment) and

Please adopt a stepwise variable selection approach starting from the full model and, documenting all steps, present the model resulting from the procedure.

B5. **Priority question**
The model results indicate that everolimus dominates axitinib with lower costs and substantially longer life expectancy. However, scientific literature and expert opinion regard axitinib to be non-inferior to everolimus in terms of effectiveness, as also noted in Section 4.10.7 of the company submission. Please provide the results of a sensitivity analysis assuming the same effectiveness profile for axitinib and everolimus (i.e. axitinib equally as effective as everolimus).

B6. Please clarify why subsequent therapies, including those which are not established clinical practice for advanced renal cell carcinoma in England, were included in the model. As these treatments are not currently reimbursed by the NHS, they do not represent a relevant cost. Please provide a scenario analysis assuming all patients receive only best supportive care (BSC) after discontinuing treatment.

B7. Please describe in detail what part of the terminal care costs are not direct costs to the NHS. Please provide an estimate of the terminal care costs (before and after adjusting for inflation) only for the costs relevant under the perspective stated in the NICE Reference Case.

B8. Please provide a sensitivity analysis using independently assessed progression (as opposed to outcomes assessed by investigators) from the CheckMate 025 trial.

Section C: Textual clarifications and additional points

C1. Please verify the accuracy of the AIC and BIC values reported in Table 35, page 152 of the company submission.

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Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

Dear Dr Goodall,

Please find enclosed Bristol Myers Squibb's response to the clarification questions from the Evidence Review Group, BMJ Evidence, received on the 21 March 2016.

Alongside this response we have also provided clinical study reports as requested and 7 additional references supporting this response.

Please let me know if you have any additional questions.

Yours sincerely

[redacted]

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Section A: Clarification on effectiveness data

A1. **Priority question**
Please provide the Clinical Study Reports for CheckMate 025, CheckMate 010 and CheckMate 003.

Clinical Study Reports requested are provided alongside this document.

A2. Please provide information of any recent updates to the literature search originally performed in November 2014.

Updates to the systematic searches were initiated on 1 January 2016. A total of 1,624 additional records were identified through electronic database searches. After removal of duplicates (n=19), primary screening was carried out on 1,605 records. Of these, 1,522 were excluded as they were clearly not of relevance to the research question; of the 83 records assessed in full, 27 reported results for studies meeting the eligibility criteria of the review. Conference proceeding searches identified an additional four abstracts that also met the eligibility criteria of the review. A PRISMA flow diagram and references for all papers identified in the review update are provided in Appendix A2.

In summary, two further randomised controlled trials (RCT) were identified: the METEOR trial investigating the comparative efficacy of cabozantinib and everolimus[1]; and a California Cancer Consortium (CCC) trial investigating the comparative efficacy of TRC105 plus bevacizumab and bevacizumab monotherapy.[2] In addition, the following RCTs that were identified through early publication in the original review have since been published in full:

- DISRUPTOR-1: active controlled trial investigating the clinical efficacy of BNC105P plus everolimus versus everolimus[3]
- ESPN: sequencing trial investigating the clinical efficacy of everolimus followed by sunitinib and vice versa (population of non-clear cell histology)[4]
- Motzer et al. 2015: active controlled trial investigating the clinical efficacy of lenvatinib versus everolimus versus lenvatinib plus everolimus)[5]
- Qin et al. 2012: active controlled trial investigating the clinical efficacy of axitinib versus sorafenib (population of Asian ethnicity)[6]
- SWITCH sequencing trial investigating the clinical efficacy of sunitinib followed by sorafenib and vice versa[7]

Importantly, no additional trials were identified that provide data of direct relevance to the decision problem. Furthermore, the inclusion of any of the active controlled trials in the network meta-analysis (NMA) would not markedly influence original estimates of comparative efficacy. Each would only be connected on the periphery of the network as ‘spider-arms’ (if considered suitable for inclusion) and as recognised by the NICE decision support unit (DSU), would therefore add no further information to the synthesis comparator set.[8]

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A3. Please clarify whether in CheckMate 025, disease assessment was done independently and if so please provide the data.

Disease assessment was not conducted independently in CheckMate 025. This trial was designed with a primary endpoint of overall survival which is not a subjectively assessed outcome. Independent review of surrogate markers for long-term benefit was not deemed necessary, in line with regulatory authority guidelines where independent review and confirmation of best tumour response and progression are only requested if progression-free survival is the primary endpoint.[9]

A4. Using the table below, please provide the baseline characteristics of UK patients in CheckMate 025.

Characteristics	**Nivolumab (n=14)**	**Everolimus (n=12)**
Age, median (range), years	58.5 (42-74)	62.0 (53-82)
Gender, male n (%)	12 (85.7)	10 (83.3)
Caucasian, n (%)	13 (92.9)	12 (100)
MSKCC risk group, n (%)		
Favourable	4 (28.6)	5 (41.7)
Intermediate	8 (57.1)	5 (41.7)
Poor	2 (14.3)	2 (16.7)
Karnofsky PS, n (%)		
80	5 (35.7)	2 (16.7)
90	4 (28.6)	6 (50.0)
100	5 (35.7)	4 (33.3)
Median (range) time from initial diagnosis to randomisation, years	4.64 (0.9-21.8)	5.48 (0.7-25.2)
Previous antiangiogenic regimens for treatment of advanced RCC, n (%)		
1	11 (78.6)	11 (91.7)
2	2 (14.3)	1 (8.3)
>2 (off protocol)	1 (7.1)	0

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Characteristics	Nivolumab (n=14)	Everolimus (n=12)
Previous systemic therapy for metastatic RCC, n (%)		
Sunitinib	8 (57.1)	10 (83.3)
Pazopanib	9 (64.3)	1 (8.3)
Axitinib	0	0
PD-L1 expression level, n (%)		
≥1%	3 (25.0)	1 (8.3)
<1%	9 (75.0)	11 (91.7)
≥5%	2 (16.7)	0
<5%	10 (83.3)	12 (100)

A5. Please clarify why quality of life was assessed with FKSIDRS rather than FKSI-15, given FKSIDRS is a subscale of FKSI-15.

FKSI-DRS was chosen in preference to FKSI-15 for the CheckMate 025 study to minimise the burden on participants in completing questionnaires, given the study also included the EQ-5D instrument.

A6. Please clarify why a full systematic review for non-RCT evidence was not considered necessary.

RCTs are the preferred source for synthesis of evidence on health effects which should be based on data of the best available quality.[10] RCT data are available for all comparators named in the decision problem, and therefore non-RCT data were not required for estimates of comparative efficacy and subsequent cost-effectiveness. Such a sequencing approach to study type is acknowledged by NICE to prevent unnecessary searching and review work.[11]

The only non-RCT data that were considered relevant to the decision problem were the clinical efficacy data for nivolumab (CheckMate 003 and CheckMate 010), which is not available for the treatment of advanced RCC outside of BMS sponsored trials. In line with NICE guidance that states “when all published or unpublished clinical data are within the company’s possession, custody or control – a systematic literature search may not be necessary”[12], a systematic review of non-RCT data was therefore not considered necessary. It is also important to recognise that these data were only presented as support for RCT evidence; they were not utilised in estimates of comparative efficacy or subsequent cost effectiveness, and therefore the value of conducting a full systematic review for non-RCT evidence was considered minimal.

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A7. For each of the trials included in the network, please state which treatments patients had received before entering the trial, including the proportion (number and percent) of patients who had each of these treatments. Please provide this information in the table below.

Trial	Prior treatment(s), n (%)[a]	
CheckMate 025	**Nivolumab (n=410):** VEGF targeted, 410 (100): • Sunitinib, 246 (60); • Pazopanib, 119 (29); • Axitinib: 51 (12) Cytokines, 68 (17)	**Everolimus (n=411):** VEGF targeted, 411 (100): • Sunitinib, 242 (59); • Pazopanib, 131 (32); • Axitinib, 50 (12) Cytokines, 74 (18)
AXIS	**Axitinib (n=361):** Sunitinib, 194 (54); Cytokines, 126 (35); Bevacizumab, 29 (8); Temsirolimus, 12 (3)	**Sorafenib (n=362):** Sunitinib, 195 (54); Cytokines, 125 (35); Bevacizumab, 30 (8); Temsirolimus, 12 (3)
GOLD	**Dovitinib (n=284):** VEGF targeted, 284 (100): • Sunitinib, 260 (92); • Bevacizumab, 10 (4); • Axitinib, 3 (1); • Pazopanib, 10 (4) mTOR inhibitor, 284 (100): • Everolimus, 247 (87); • Temsirolimus, 35 (12) Nephrectomy, 272 (96); Radiotherapy, 66 (23); Cytokines, 20 (7)	**Sorafenib (n=286):** VEGF targeted, 286 (100): • Sunitinib, 253 (88); • Bevacizumab, 11 (4); • Axitinib, 6 (2); • Pazopanib, 11 (4) mTOR inhibitor, 286 (100); • Everolimus, 247 (86); • Temsirolimus, 39 (14) Nephrectomy, 260 (91); Radiotherapy, 91 (32); Cytokines, 23 (8)
INTORSECT	**Total population (n=512):** Sorafenib, 512 (100)	
RECORD-1	**Everolimus + BSC (n=277):** Sunitinib only, 124 (45); Sorafenib only, 81 (29); Sunitinib + sorafenib, 72 (26); Immunotherapy: 179 (65); Chemotherapy: 37 (13); Hormone therapy: 5 (2); Radiotherapy: 85 (31); Nephrectomy: 269 (97)	**Placebo + BSC (n=139):** Sunitinib only, 60 (43); Sorafenib only, 43 (31); Sunitinib + sorafenib, 36 (26); Immunotherapy:93 (67); Chemotherapy: 22 (16); Hormone therapy: 5 (4); Radiotherapy: 38 (27); Nephrectomy: 133 (96)
RECORD-3	**Everolimus (n=238):** Sunitinib, 238 (100)[a]	**Sunitinib (n=233):** Everolimus, 233 (100)[a]

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Trial	Prior treatment(s), n (%)[a]		
TARGET	**Sorafenib (n=451):** Cytokine based, 374 (83); IL-2, 191 (42); IFN, 307 (68); IL-2 + IFN, 124 (27); Radiotherapy, 124 (27); Nephrectomy, 422 (94)	**Placebo (n=452):** Cytokine based, 368 (81); IL-2, 189 (42); IFN, 314 (69); IL-2 + IFN, 135 (30); Radiotherapy, 108 (24); Nephrectomy, 421 (93)	
TIVO-1	-	-	
VEG105192	**Total population (n=435):** Cytokines, 435 (100)		
Yang et al 2003	**Bevacizumab 10mg (n=39):** IL-2, 37 (94.8); Chemotherapy, 10 (25.6); Radiotherapy, 8 (20.5); Nephrectomy, 35 (89.7)	**Bevacizumab 3mg (n=37):** IL-2, 34 (91.9); Chemotherapy, 7 (18.9); Radiotherapy, 6 (16.2); Nephrectomy, 33 (89.2)	**Placebo (n=40):** IL-2, 37 (92.5); Chemotherapy, 8 (20); Radiotherapy, 12 (30); Nephrectomy, 38 (95)

Key: IFN, interferon; IL-2, interleukin-2; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

Notes: [a], patients may have received more than one prior treatment.

Source: Escudier et al. 2007[13];Hutson et al. 2014[14];Motzer et al. 2008[15];Motzer et al. 2013[16];Motzer et al. 2014[17]; Motzer et al. 2014[18];Motzer et al. 2015[19]; Rini et al. 2011[20];Sternberg et al. 2010[21]; Yang et al. 2003.[22]

A8. Please provide the Kaplan Meier curves and estimates of progression-free survival and overall survival from CheckMate 025 (as mean and median times, including standard deviation and confidence intervals) for nivolumab and everolimus (separately) based on previous treatment with a tyrosine kinase inhibitor or cytokine (i.e. 4 Kaplan Meier curves for progression-free survival and 4 Kaplan Meier curves for overall survival in total).

To clarify, prior cytokine therapy was allowed in CheckPoint 025, however, patients had to have had at least one prior anti-angiogenic therapy to be eligible for the study. Therefore, there was no patient subgroup in the study that received only cytokine therapy prior to study entry. We have therefore provided the curves requested for two patient populations; patients with one prior therapy where this was an anti-angiogenic and patients with two prior therapies where these were a cytokine and an anti-angiogenic.17% (142 of 821) of patients received cytokine treatment as one of their prior therapies. Table 1 shows OS and PFS results for these subgroups.

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Table 1: OS and PFS by prior therapy subgroups

Prior therapy	Nivolumab n=410	Everolimus n=411	Total n=821
No. of patients:			
Cytokine + anti-angiogenic	68	74	142
Anti-angiogenic only	342	337	679
mOS (months):			HR
Cytokine + anti-angiogenic	27.37 (95%CI, 26.71,NA)	24.67 (95%CI, 16.03, NA)	0.64 (95%CI, 0.38,1.09)
Anti-angiogenic only	23.23 (95%CI, 20.70,NA)	19.09 (95%CI, 17.48, 21.55)	0.77 (95%CI, 0.63, 0.96)
mPFS (months):			HR
Cytokine + anti-angiogenic	4.21 (95% CI; 2.04,5.55)	3.71 (95% CI; 2.10,7.36)	0.91 (95% CI; 0.62,1.32)
Anti-angiogenic only	4.60 (95% CI; 3.71,5.52)	4.50 (95% CI; 3.75,5.52)	0.87 (95% CI; 0.73,1.03)

Appendix A8 shows the Kaplan Meier plots for PFS and OS for patients with one prior anti-angiogenic therapy and patients with two prior therapies, a cytokine and an anti-angiogenic therapy.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**
Please clarify how events are defined in the time to discontinuation (TTD) survival analysis, and in particular, clarify if patients who die are considered to discontinue treatment or are censored.

In the TTD survival analysis, events were defined as treatment discontinuations for any reason, including death; therefore deaths were considered as treatment discontinuations not censored events. The TTD survival analysis presented is analogous to what is sometimes described as time-on-treatment survival analysis.

B2. **Priority question**
Please clarify the clinical reason why the utility scores for patients in the post-progression health state would be different based on the treatment received (that is, nivolumab or everolimus).

As described in Section 5.4.2, higher post-progression EQ-5D utility estimates were observed for nivolumab patients versus everolimus patients in CheckMate 025, and this was reasoned to be due to two main factors.

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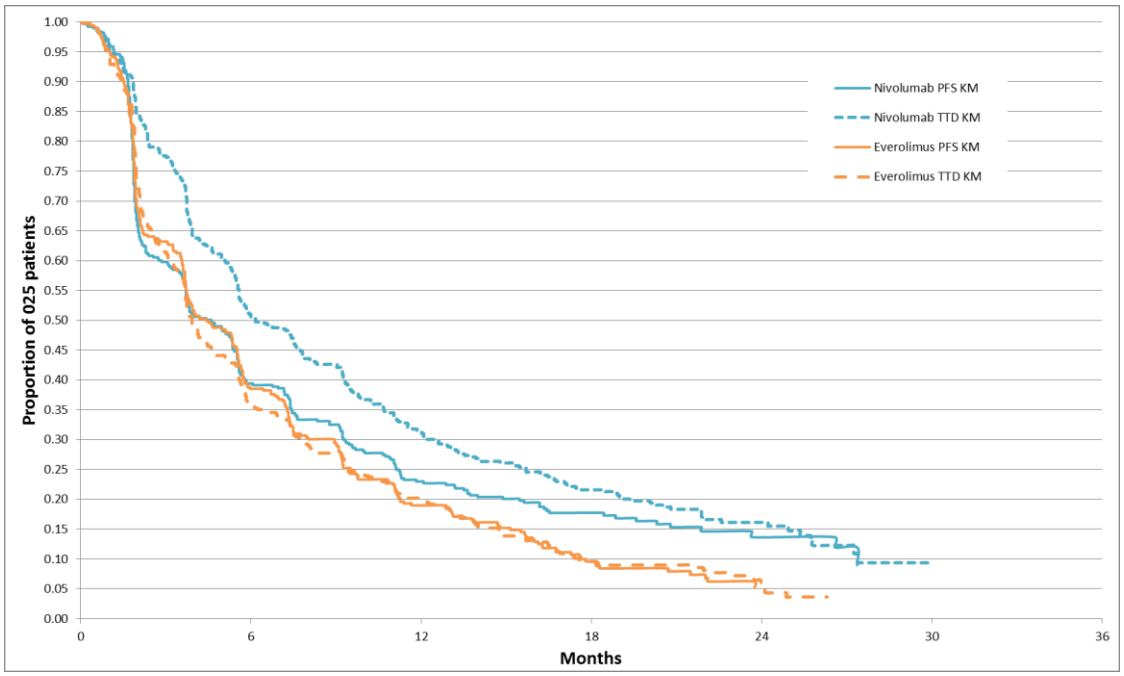
First, treatment was allowed beyond progression in both arms of CheckMate 025, and as shown in Figure 39 of the submission dossier and replicated below in Figure 1, patients in the nivolumab arm spent significantly longer receiving active treatment beyond RECIST-defined progression. As such, average post-progression utility would be expected to be higher for patients who receive nivolumab than for patients who receive everolimus.

Figure 1: KM PFS and TTD data, CheckMate 025



Key: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

The second factor explaining a post-progression health-related quality of life (HRQL) benefit for nivolumab patients is linked to the first, but concerns the period after treatment discontinuation. As previously described, the immune-response mechanism of nivolumab implies benefit both beyond RECIST-defined progression and beyond treatment discontinuation. Figure 13 of the submission showed reductions in target lesion tumour burden in CheckMate 025 to appear deeper in the nivolumab group compared to the everolimus group.

CheckMate 025 data are insufficient to demonstrate the long-run survival benefits expected by clinicians[23] because OS data for patients randomised to nivolumab were less than 60% complete at last point of follow-up. However, evidence for IL-2 cytokine immunotherapy in advanced RCC[24, 25], nivolumab in melanoma patients (NICE ID845) and other immune-response cancer therapies[26], suggest clinical expectations of an immune-response-based long-run OS plateau are justified.

As well as extending life, this post-treatment, post-progression benefit is reasoned to improve HRQL. By reducing the burden of disease symptoms, immune-response disease suppression is highly likely to improve patient HRQL for post-progressive patients. In

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addition, as described in Section 5.4 of the submission, patient quality of life is affected by thoughts of the future and ongoing treatment effectiveness.[23] [27] For post-progressive patients, the evidence and clinical expectation of the post-progression, post-treatment immune-response benefit of nivolumab may afford hope. This hope may be very valuable indeed.

B3. **Priority question**
Please provide further justification for assuming that patients treated with axitinib would have a HRQoL utility score lower than patients who receive nivolumab or everolimus, irrespective of their disease progression status.

As described in the submission, we followed NICE guidance in using patient-reported EQ-5D data to capture patient utility. For nivolumab and everolimus, these data are from patients in the pivotal CheckMate 025 trial. For axitinib patients, these data are from the patients in the AXIS study and were used to inform decision-making in TA333. As such, each were collected in the same patients as the key effectiveness data.

As noted, these data suggest that axitinib patients have lower utility than both nivolumab patients and everolimus patients, irrespective of disease-progression status. There are no studies directly comparing HRQL across axitinib patients and nivolumab or everolimus patients, in the same way that there are no direct comparative data for other clinical outcomes for axitinib versus either everolimus or nivolumab. There is, however, evidence and rationale to support the implications arising from taking the NICE reference case approach.

The EQ-5D evidence suggesting patients treated with nivolumab have better HRQL than patients treated with axitinib is supported by reason and further evidence. First, across the two key trials, a higher overall response rate was observed for nivolumab (25%) than that achieved with axitinib (19%).

Second, as illustrated in Table 26 of Section 4.12 in the submission, the tolerability profile for nivolumab appears better than for axitinib. Treatment-emergent diarrhoea was experienced by over 50% of axitinib patients in the AXIS study, and treatment-emergent hypertension by over 40% of axitinib patients. Three further treatment-emergent adverse events (AEs) were experienced by over 30% of axitinib patients (fatigue, decreased appetite and nausea), while dysphonia, hand-foot syndrome and hypothyroidism each emerged in over 20% of axitinib patients. By contrast, only one treatment-emergent AE, fatigue, presented in over 30% of nivolumab patients in CheckMate 025, and no other treatment-emergent AE presented in over 20% of patients. Rates of Grade III/IV AEs were higher in axitinib patients than nivolumab patients for all treatment-related AEs occurring in at least 10% of patients in either trial.

Third, but related to the tolerability profile of axitinib, axitinib is initiated at 5mg twice daily and escalated to an acceptable tolerability limit. This method of treatment, that pushes patients to their tolerability limit, may explain the relatively low HRQL scores of axitinib

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patients; this was cited as an important issue for axitinib patient HRQL by one experienced clinical expert during a documented clinical validation meeting.[23]

The responses to question B2 explain why evidence suggesting nivolumab patients have better HRQL than axitinib patients beyond treatment discontinuation and following discontinuation is expected. The immune-response mechanism of nivolumab means that patients experience a longer response to treatment and longer treatment duration, and beyond that, are afforded the chance of post-treatment and post-progression disease suppression, and hope for an extension in life.

The EQ-5D evidence suggests that patients treated with everolimus have better HRQL than patients treated with axitinib. While this is the best evidence for decision making, the supporting evidence for this is less overwhelming than for nivolumab versus axitinib. Evidence from key studies suggest that the overall response rate associated with axitinib is higher in the AXIS study than that seen with everolimus in CheckMate 025. In addition, everolimus has a more favourable toxicity profile to axitinib, as demonstrated in Section 4.12 of the submission. Again, the dose escalation mechanism of axitinib highlighted by an experienced clinical expert as a key issue for HRQL in axitinib treated patients, may explain the observed differences in utility in that evidence base.

In summary, the utility data used in the base case were selected to follow NICE guidance on using patient-reported EQ-5D data to capture patient utility. To explore the importance of the implied difference in patient utility across axitinib and everolimus patients, we included a scenario in Section 5.8.3 of the submission that assumed axitinib patient utility was equal to everolimus patient utility.

B4. **Priority question**

a. Please clarify why treatment status (i.e. on treatment or off treatment) was not taken into account in the mixed model for the CheckMate 025 EQ-5D data analysis.

The mixed model specification was designed based on the key clinical drivers of patient utility and the available data, but your suggestion to explore the inclusion of treatment status variables and interaction terms is reasonable, and we are happy to present these in our response to part b.

b. Please test the interactions between the variables and fit of a model including:

   i. treatment allocation (nivolumab or everolimus),

   ii. disease progression status (not progressed or progressed),

   iii. treatment status (on treatment and off treatment) and

   Please adopt a stepwise variable selection approach starting from the full model and, documenting all steps, present the model resulting from the procedure.

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Table 2 presents results from a stepwise approach to variable selection, starting from the full model. Model 6 is identical to the model used in the base case analysis; goodness-of-fit statistics show this model to provide the best fit to the data, and justify its use in the base case analysis.

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Table 2: Model results from stepwise variable selection approach to mixed model analysis of CheckMate 025 EQ-5D data

Parameters/Fit Statistics	Model 1: Full Model, Mean (SE), p-value	Model 2: Treatment Arm Dropped, Mean (SE), p-value	Model 3: Progression Status Dropped, Mean (SE), p-value	Model 4: Treatment Arm Added, Mean (SE), p-value	Model 5[2]: Treatment Status Dropped, Mean (SE), p-value	Model 6: Progression Status Added, Mean (SE), p-value
Intercept[1]	0.799 (0.021), <0.001	0.781 (0.008), <0.001	0.767 (0.007), <0.001	0.785 (0.011), <0.001	0.763 (0.011), <0.001	0.798 (0.010), <0.001
Treatment Arm (Everolimus)	-0.037 (0.015), 0.014	-	-	-0.036 (0.015), 0.013	-0.033 (0.014), 0.018	-0.036 (0.015), 0.017
Progression Status (Progression)	-0.024 (0.009), 0.008	-0.025 (0.007), <0.001	-	-	-	-0.069 (0.007), <0.001
Treatment Status (Off treatment)	-0.052 (0.014), <0.001	-0.057 (0.012), <0.001	-0.083 (0.005), <0.001	-0.091 (0.007), <0.001	-	-
Treatment Arm*Progression Status	-0.005 (0.014), 0.699	-	-	-	-	0.005 (0.010), 0.654
Progression Status*Treatment Status	-0.038 (0.017), 0.029	-0.014 (0.014), 0.312	-	-	-	-
Treatment Arm*Treatment Status	-0.015 (0.025), 0.543	-	-	0.018 (0.010), 0.083	-	-
Treatment Arm*Progression Status*Treatment Status	0.055 (0.029), 0.062	-	-	-	-	-
Goodness-of-fit statistics						
-2 Residual Log Likelihood	-5233.9	-5244.8	-5212.8	-5206.8	-5118.7	-5308.3
AIC	-5227.9	-5238.8	-5206.8	-5200.8	-5112.7	-5302.3
AICc	-5227.9	-5238.8	-5206.8	-5200.7	-5112.7	-5302.3
BIC	-5214.1	-5225.0	-5192.8	-5186.8	-5098.6	-5288.5

Key: AIC, Akaike Information Criterion; AICc, AIC correction; BIC, Bayesian Information Criterion; SE, standard error.

Generally, mixed models included EQ-5D Utility Index Score as a dependent measure, with the fixed effects of treatment arm, treatment status and progression status. Subject was treated as random effect. A compound symmetry covariance structure was used unless otherwise noted.

[1] Intercept includes nivolumab treatment arm, on treatment treatment status and non-progression (SD/PR/CR) progression status.

Model 1 included all main effects, all 2 variable and 3 variable interactions. All subsequent models removed main effects and interactions in a stepwise manner.

[2] Model 5 used an autoregressive covariance structure.

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B5. **Priority question**

The model results indicate that everolimus dominates axitinib with lower costs and substantially longer life expectancy. However, scientific literature and expert opinion regard axitinib to be non-inferior to everolimus in terms of effectiveness, as also noted in Section 4.10.7 of the company submission. Please provide the results of a sensitivity analysis assuming the same effectiveness profile for axitinib and everolimus (i.e. axitinib equally as effective as everolimus).

As described in Section 4.10.7 of the submission dossier, the base case NMA follows NICE DSU technical support document guidance. In the absence of any data directly comparing clinical outcomes across everolimus and axitinib patients, the NMA is considered the best available reflection of expected survival outcomes for patients in English clinical practice and the appropriate basis for decision-making.

For comparison with results from scenarios explored here and in responses to questions B6 and B7, base case results are presented in Table 3.

Data and clinical opinion suggesting similar clinical outcomes for everolimus and axitinib are broadly limited to PFS, and these data sources bear recognised limitations. As there are no direct head-to-head evidence comparing axitinib with everolimus, it is far from certain that axitinib is non-inferior to everolimus. The most recent analysis to compare clinical outcomes across everolimus and axitinib used a weight-adjusted indirect comparison of PFS using data from Record-1 and AXIS trials, respectively.[28] The results showed no significant difference in PFS across everolimus and axitinib, and these findings are consistent with results from our NMA. However, to understand the implications of assuming identical PFS across everolimus and axitinib, results from a scenario in which axitinib PFS is assumed identical to everolimus PFS are shown in Table 4. The key incremental cost-effectiveness ratio (ICER) versus axitinib is lower than in the base case, due to the treatment costs incurred by pre-progressive axitinib patients.

Table 5 shows results from an additional scenario in which both PFS and OS for axitinib patients are assumed to be identical to everolimus patients, as captured by CheckMate 025 comparator arm data. While these results may be useful in considering the sensitivity of the model to key assumptions, we stress that these results should not be used in the base case; the NMA analyses presented are the most plausible and preferable from a methodological perspective. The ICER versus axitinib increases to less than £47,225; nivolumab remains cost effective at a willingness-to-pay threshold of £50,000 per quality-adjusted life year (QALY) gained.

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Table 3: Base-case results; pairwise analysis, nivolumab versus comparator

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£46,133.83	1.25	2.09	£45,218.83	1.07	1.35	£42,417.26
Everolimus	£38,920.38	1.69	2.55	£52,432.28	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,827.72	1.43	1.97	£56,427.43
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

Table 4: Scenario; assume axitinib PFS equal to everolimus PFS

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£50,791.97	1.26	2.09	£40,560.70	1.06	1.35	£38,399.59
Everolimus	£38,920.38	1.69	2.55	£52,432.28	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,827.72	1.43	1.97	£56,427.43
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

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Table 5: Scenario; assume axitinib PFS and OS equal to everolimus PFS and OS

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£52,698.24	1.49	2.55	£38,654.42	0.82	0.89	£47,215.69
Everolimus	£38,920.38	1.69	2.55	£52,432.28	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,827.72	1.43	1.97	£56,427.43
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

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B6. Please clarify why subsequent therapies, including those which are not established clinical practice for advanced renal cell carcinoma in England, were included in the model. As these treatments are not currently reimbursed by the NHS, they do not represent a relevant cost. Please provide a scenario analysis assuming all patients receive only best supportive care (BSC) after discontinuing treatment.

A scenario assuming equivalent subsequent treatment costs across active treatment model arms was presented in Section 5.8.3 of the submission, but as you suggest, a scenario in which no subsequent therapy costs are assumed may also be useful for decision-making. Results from this scenario are presented in Table 6; consistent with the scenario explored in the submission dossier, this assumption is not an important driver of results in the key comparison to axitinib.

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Table 6: Scenario; assume patients receive BSC only after treatment discontinuation

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£85,223.35	2.31	3.44				
Axitinib	£38,209.77	1.25	2.09	£47,013.58	1.07	1.35	£44,100.82
Everolimus	£30,798.76	1.69	2.55	£54,424.59	0.63	0.89	£87,014.56
BSC	£10,524.94	0.88	1.47	£74,698.40	1.43	1.97	£52,148.43
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

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B7. Please describe in detail what part of the terminal care costs are not direct costs to the NHS. Please provide an estimate of the terminal care costs (before and after adjusting for inflation) only for the costs relevant under the perspective stated in the NICE Reference Case.

The King's Fund study estimate of the cost of terminal care for UK cancer patients (£5,401 in 2007/8; £6,160 after adjusting to 2014/15 costs[29]) is reported in a retrospective descriptive analysis of the impact of services introduced in 2004 to increase choice at the end of life for cancer patients in Lincolnshire.[30] Parts of these services are funded by the voluntary sector, though the proportion of the total cost attributable to the voluntary sector is not reported. Using the total cost estimate can be considered appropriate because the voluntary sector are arguably picking up responsibility that falls within the remit of the NHS/PSS. Furthermore this estimate has been used to inform decision making in numerous previous NICE TAs, including TA359, completed in 2015.

Importantly, any uncertainty around the proportion of terminal care costs that are borne by the NHS/PSS is not pivotal for model results. Table 7 shows results from a scenario in which 50% of the King's Fund estimate of terminal care costs are assumed within-scope; the key ICER versus axitinib deviates from the base case by less than £100.

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Table 7: Assume 50% of King's Fund estimate of terminal cancer care costs are direct NHS/PSS costs

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£88,582.15	2.31	3.44				
Axitinib	£43,270.23	1.25	2.09	£45,311.93	1.07	1.35	£42,504.59
Everolimus	£36,086.76	1.69	2.55	£52,495.40	0.63	0.89	£83,930.16
BSC	£7,628.89	0.88	1.47	£80,953.26	1.43	1.97	£56,515.07
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

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B8. Please provide a sensitivity analysis using independently assessed progression (as opposed to outcomes assessed by investigators) from the CheckMate 025 trial.

As described in the response to A3, the primary endpoint of this study was OS, and an independent review committee was not utilised, therefore this analysis is not possible.

Section C: Textual clarifications and additional points

C1. Please verify the accuracy of the AIC and BIC values reported in Table 35, page 152 of the company submission.

Please accept our apologies for what was a copy error in the submission dossier. Table 8 shows accurate AIC and BIC statistics for spline model fits to PFS data for patients randomised to nivolumab in CheckMate 025.

The copy error also had implications for the data in Table 36 of the submission dossier, showing AIC and BIC statistics for spline model fits to PFS data for patients randomised to everolimus in CheckMate 025. Table 9 shows accurate AIC and BIC statistics for these model fits.

Table 8: AIC and BIC statistics, Spline model fits to stratified PFS data, nivolumab arm, CheckMate 025

Model	AIC	Model	BIC
Spline 2 knot(s) – odds	1897.302	Spline 2 knot(s) - odds	1913.367
Spline 2 knot(s) – hazard	1897.665	Spline 2 knot(s) - hazard	1913.730
Spline 1 knot(s) – odds	1909.947	Spline 1 knot(s) - odds	1921.996
Spline 1 knot(s) – hazard	1915.430	Spline 1 knot(s) - hazard	1927.479
Spline 1 knot(s) – normal	1921.659	Spline 1 knot(s) - normal	1933.708
Spline 2 knot(s) – normal	1923.369	Spline 2 knot(s) - normal	1939.434

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

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Table 9: AIC and BIC statistics, Spline model fits to stratified PFS data, everolimus arm, CheckMate 025

Model	AIC	Model	BIC
Spline 2 knot(s) - hazard	1873.657	Spline 2 knot(s) - hazard	1889.731
Spline 2 knot(s) - odds	1874.493	Spline 2 knot(s) - odds	1890.568
Spline 1 knot(s) - hazard	1887.032	Spline 1 knot(s) - hazard	1899.088
Spline 1 knot(s) - normal	1887.476	Spline 1 knot(s) - normal	1899.531
Spline 2 knot(s) - normal	1889.282	Spline 1 knot(s) - odds	1902.660
Spline 1 knot(s) - odds	1890.604	Spline 2 knot(s) - normal	1905.357

Key: AIC, Akaike Information Criterion; Bic, Bayesian Information Criterion; PFS, progression-free survival.

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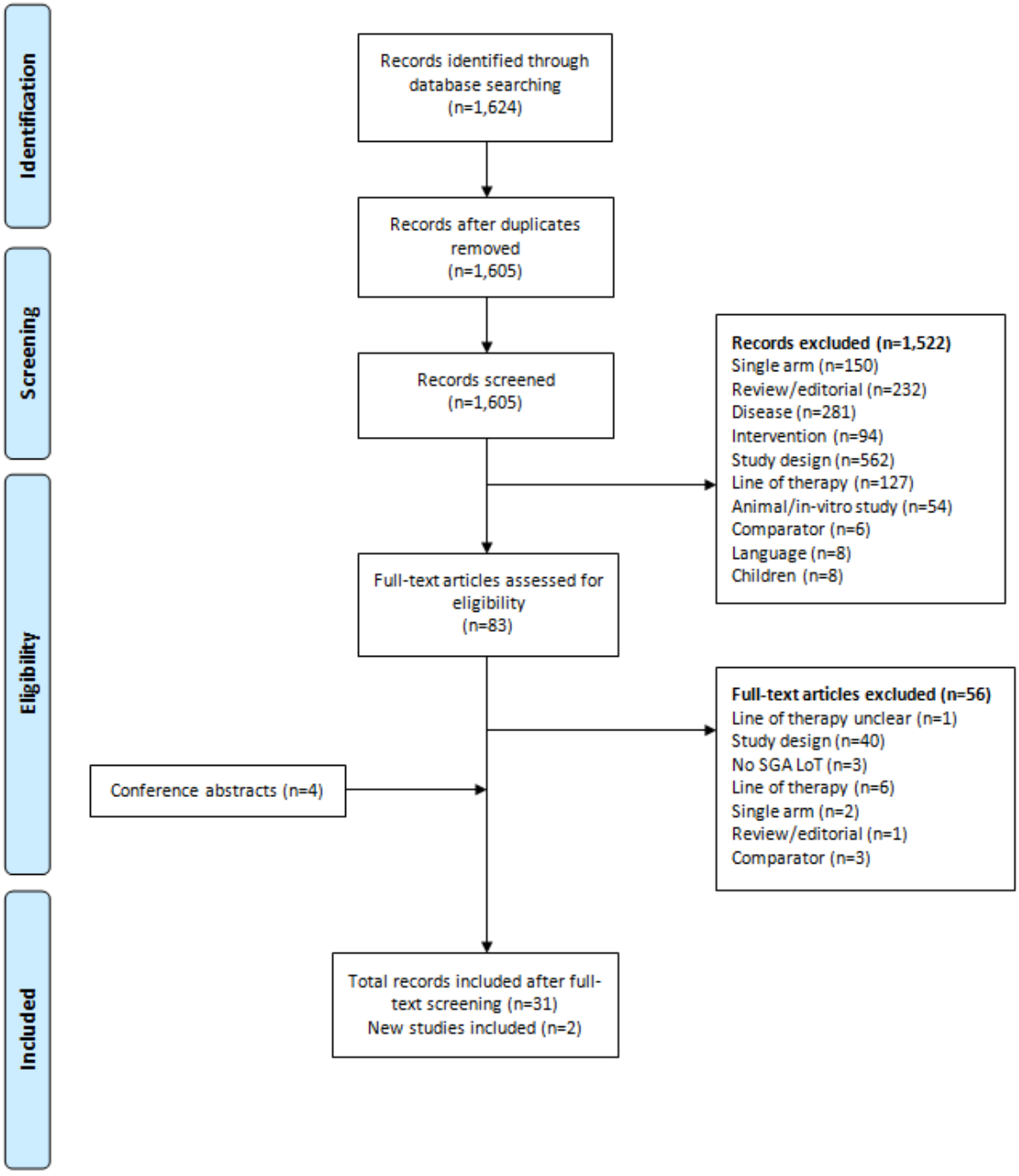
Appendix A2: PRISMA flow diagram and references for all papers identified in the review update

PRISMA flow diagram of the literature search process for update initiated in January 2016



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SGA LoT, subgroup analysis for line of therapy.

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Appendix A8: Kaplan Meier (KM) plots for PFS and OS for patients with one prior anti-angiogenic therapy and patients with two prior therapies, a cytokine and an anti-angiogenic therapy

Figure 2: KM plot for OS for patients with one prior anti-angiogenic therapy

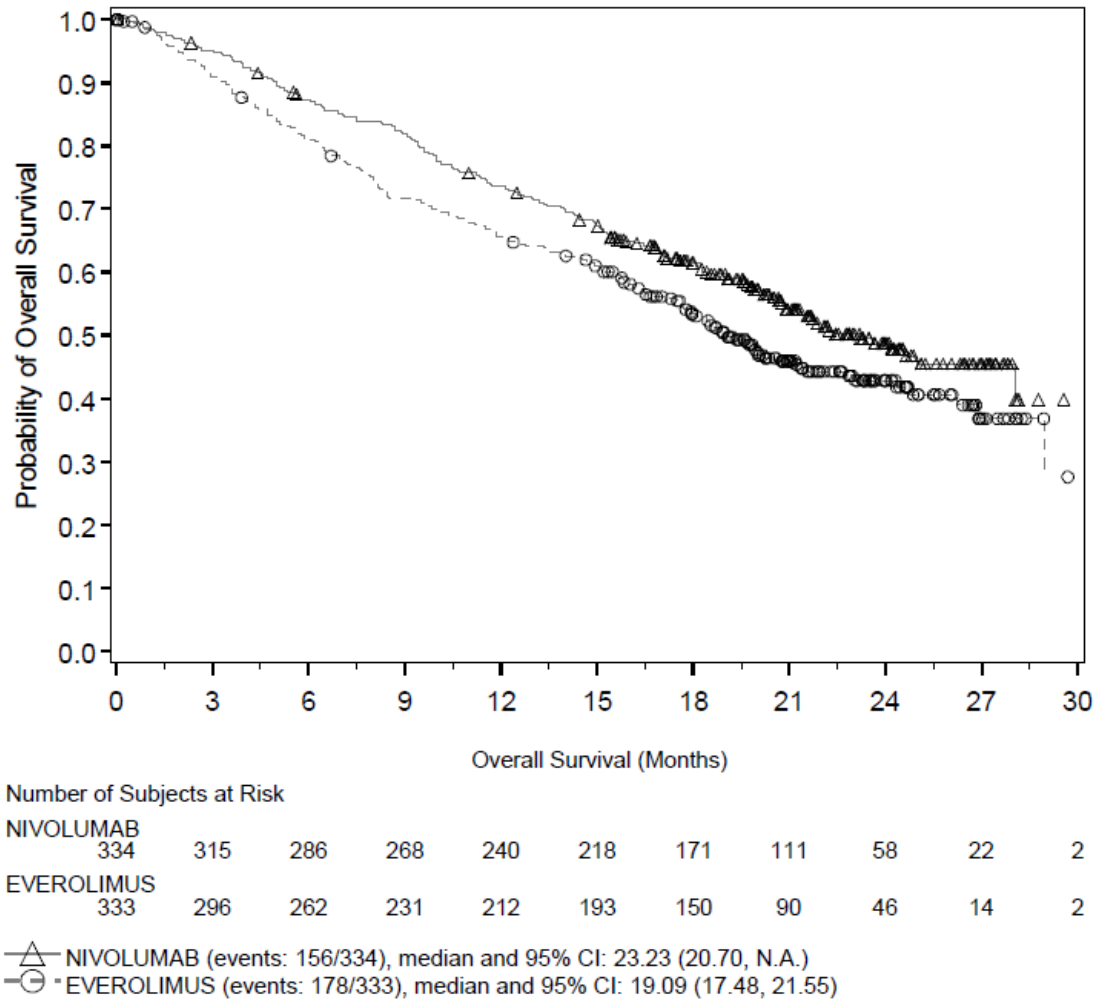

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Figure 3: KM plot for OS for patients with two prior therapies, a cytokine and an anti-angiogenic therapy

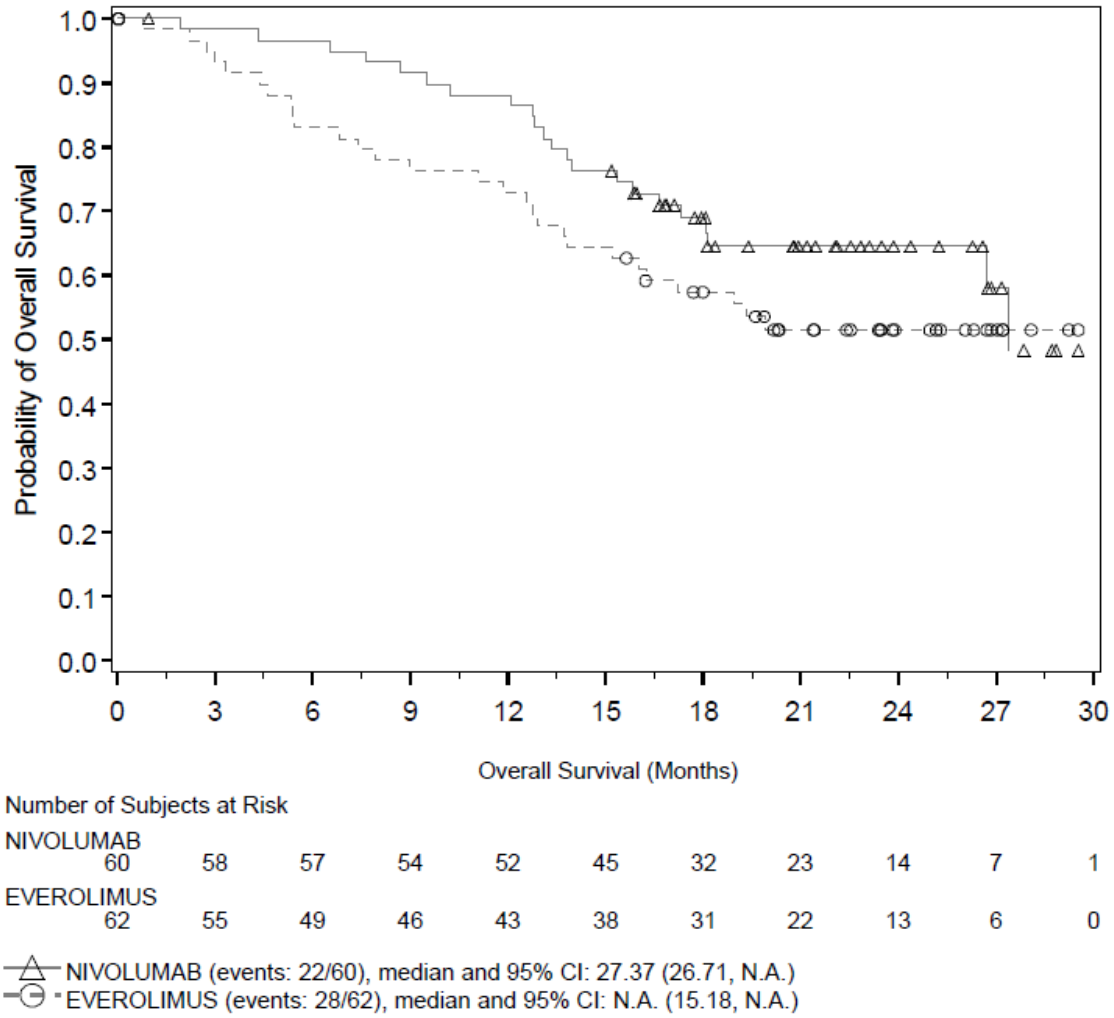

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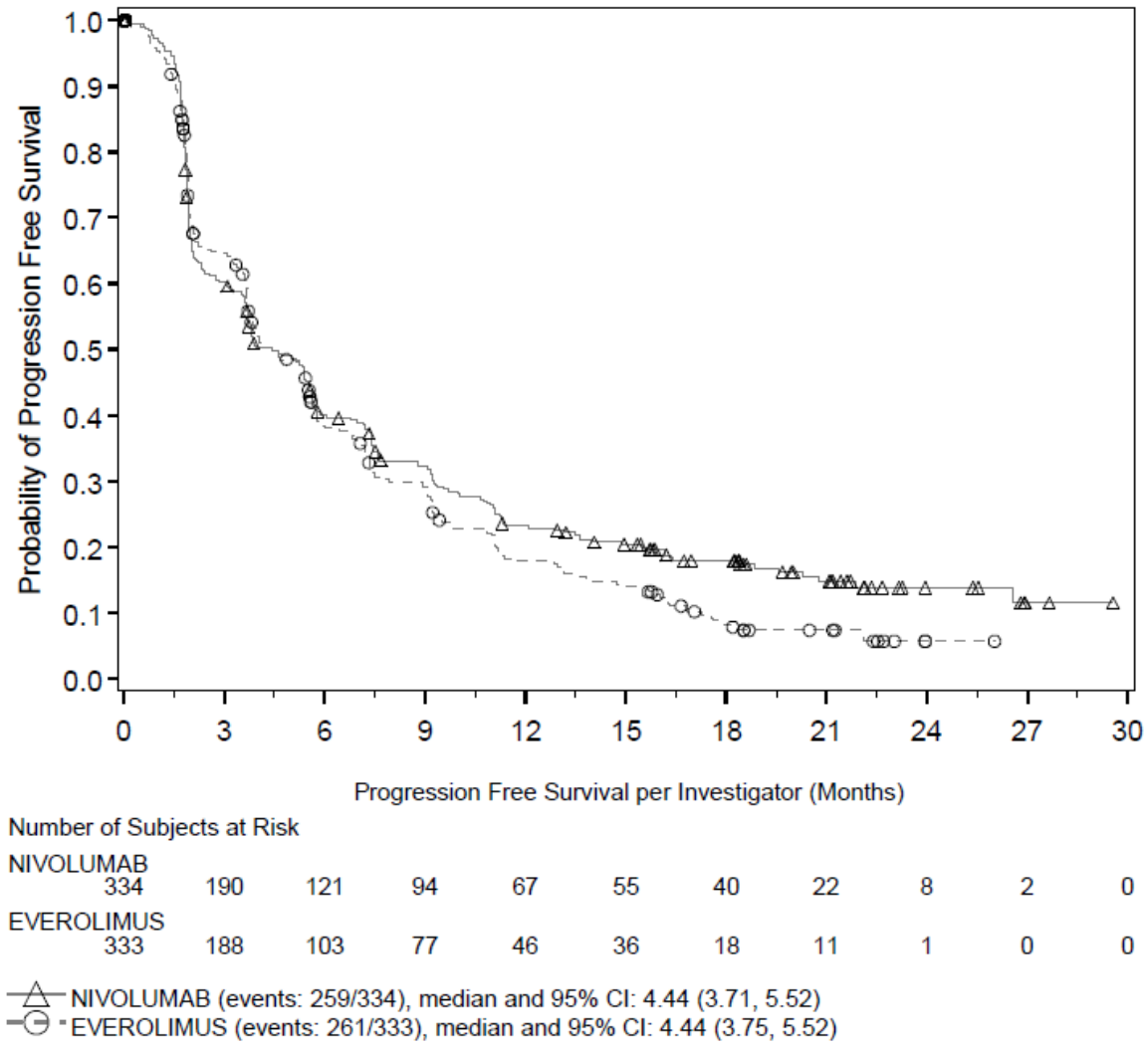
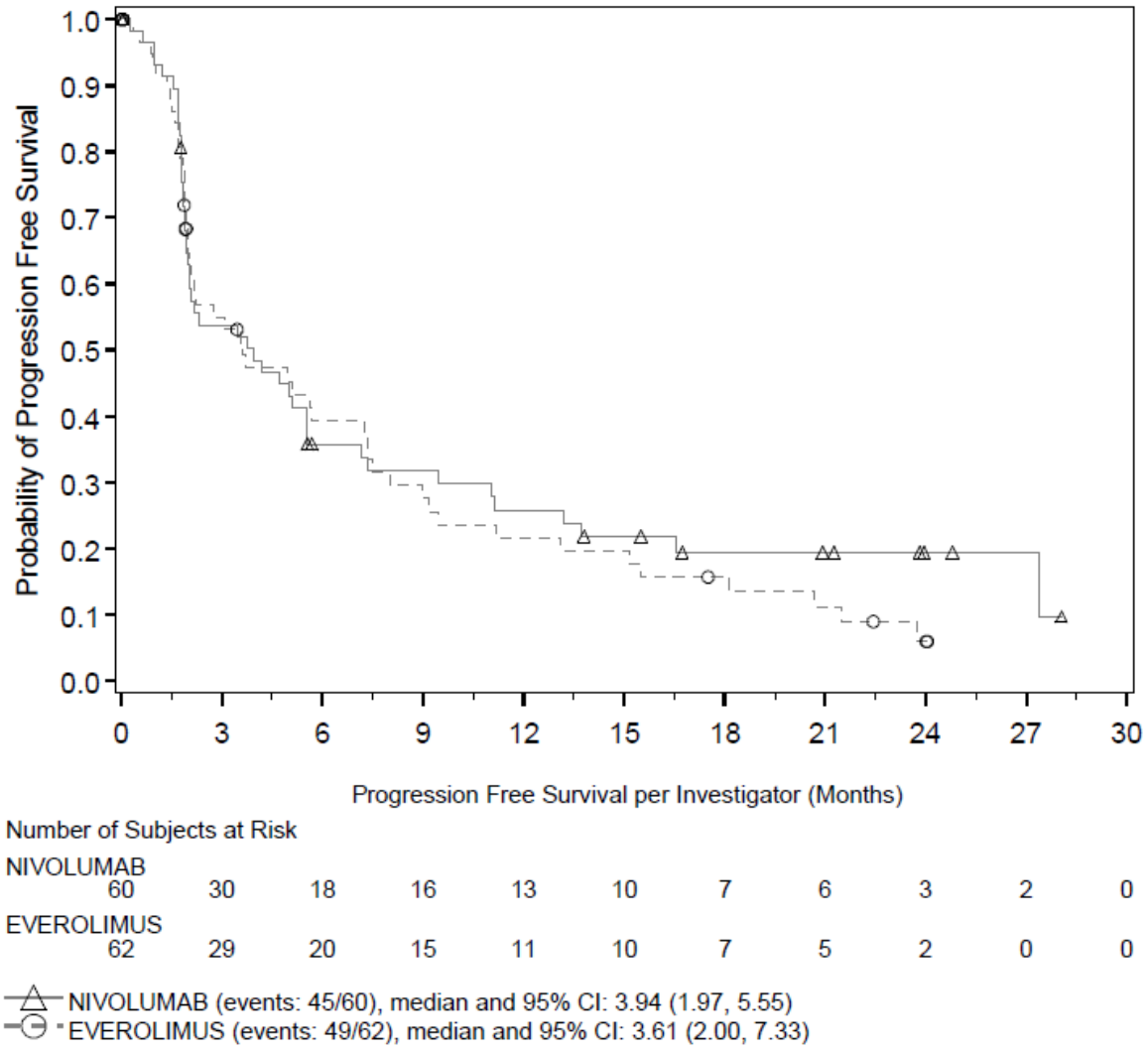
Figure 4: KM plot for PFS for patients with one prior anti-angiogenic therapy



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Figure 5: KM plot for PFS for patients with two prior therapies, a cytokine and an anti-angiogenic therapy



Kidney Cancer Support Network

The Bungalow, West Cliff, Porthtowan, Cornwall, TR4 8AE
E-mail: team@kidneycancersupportnetwork.co.uk
Office: 01209 891 307 Mobile: 07973 777 202

Website: www.kidneycancersupportnetwork.co.uk

Health Technology Appraisal

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

Kidney Cancer Support Network Statement

Nivolumab has been proven to be a clinically effective drug, and been designated a breakthrough therapy by the FDA for the treatment of advanced or metastatic renal cell carcinoma. As a breakthrough therapy, nivolumab has been fast tracked for approval in a number of countries, and was previously approved for use under the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS) in the UK.

Nivolumab is the first in a new class of immunotherapy drugs, and is already available in North America and Europe for renal cell carcinoma (RCC), and has proven to be effective in the treatment of melanoma, non-squamous non-small cell lung cancer, and Hodgkin's lymphoma. 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 immunotherapy drugs are made available to patients in order that they have the best care possible. If immunotherapy 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.

Clinicians in the UK should have the ability to choose the most effective treatments for individual patients from those available. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without nivolumab (and other immunotherapy drugs), the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the second-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second-line therapy to continue managing their disease, and to maintain quality of life.

The current second-line treatment options are not effective for everyone, and can be difficult to access. Axitinib is the only second-line treatment available to patients in England on the NHS, while funding for everolimus as a second-line treatment is available through the Cancer Drugs Fund. Undue restrictions in accessing nivolumab would simply add unnecessary additional burden to patients with a terminal diagnosis. Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Having a choice in second-line treatment 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.

A number of nivolumab clinical trials have been conducted in previously treated advanced/metastatic 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 nivolumab on the NHS, we would have to 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 drug is rejection by NICE.

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We appreciate that nivolumab is expensive, and we urge NICE and the manufacturer to negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as professional inadequacy. NICE and the manufacturer need to think outside the box to negotiate an alternative funding scheme, for example, the government could pay for those cases where nivolumab is effective, and the manufacturer should reimburse the NHS for those cases who do not respond to treatment. This will require more collaborative working with the manufacturer to negotiate an acceptable patient access scheme.

Nivolumab is the only immunotherapy drug for advanced RCC patients; other immunotherapy options are years away in development. Current treatments have proven to shrink tumours and delay disease progression in some patients, but adding nivolumab as a choice in the second-line and beyond enables patients and clinicians to have individualised treatment plans to better control their disease and maintain a high quality of life. It will also address the massive unmet need for treatment options in the third-line.

Finally, when asked to tell their stories and why access to nivolumab is so important, the following patients responded. All have accessed nivolumab via EAMS or a clinical trial. Many of their stories commented on the importance of extending life, and the improvement in quality of life that they have seen on nivolumab:

> *"In about two months the pain began to subside and very shortly ceased entirely. This was the first indication nivolumab was working. The improvement in my quality of life was of course immediate and profound. I could walk again, I could eat again, I had energy again; all of which have continued to the present day, even with the recent appearance of side effects, the effects of which really are minimal on my quality and enjoyment of life. Obviously this has impacted the life of my wife. I can now care for myself in every way and be a help to her. When I began treatment I was in a state of helplessness. The abdominal tumour was located in such a possession [sic] and was growing so fast that it caused so much pain I was unable to function. I was taking very high doses of opiate pain medication with the result that I had no appetite and combined with side effects of Sutent my weight dropped to 139 pounds from 210 pounds. I lost large amounts of muscle. As a result I was eventually confirm [sic] to a wheelchair."*
>
> *"X had four infusions before his scan last week and today had his fifth after he had his results. We have had a worrying weekend. X was on axitinib but it stopped working when he had sepsis in February so he didn't have any treatment in February and then two months of nivolumab. Dont know exact shrinkage because all his professor said was good results and X was so pleased he didn't ask any more questions."*
>
> *"……we were so lucky to get the nivolumab. They also found out that X had broken vertebrae due to osteoporosis. He has been in work full time since he was released from hospital on 15th Feb and feels really well."*
>
> *"The hope this has given me, and my family, is one of the greatest medicines in its own right, to enhance the quality of my life. The reduced overall side effects enable me to continue working full time, and to have a good quality of life…… the biggest side effect of metastasised renal cell carcinoma is death, from where I am sitting there is nothing to lose and much to gain. We understand that cost is one of the biggest barriers to the general use of Nivolumab, and other immunotherapy drugs. Here I must point out the glaringly obvious, barring a miracle, it is extremely unlikely that I will ever draw my state pension. I see no economic or ethical reason why those funds to which I have contributed to for the whole of my working life, cannot to be used to enhance and extend the remaining few year so [sic] my life. The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various farming enterprises which I manage……..I'm making a hugely positive contribution to society, and the wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities."*

Kidney Cancer Support Network

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"Seeing my families [sic] faces, my granddaughter dancing last night, her running and cuddling me afterwards is a true gift Nivolumab has given me……. Simple things like walking down the beach holding my wife's hand are simply unmeasurable [sic].……You see, it is not just my life but their lives too. My wife became my full time carer, unable to work, have a life and rarely went out of the house. UK rules means she doesn't get any benefit for this financially or otherwise. SHE HAD TO GIVE UP HER CAREER AND HASNT HAD A PENNY IN OVER 5 years. Therefore, it is not just the patient NICE should consider but also the family impact. I have recently been able to a husband, father and grandfather again. Tears abound, I am happy joyous and free for the first time in many years. Yes, the disease still exists but doesn't it too with other therapies? I wish they wouldn't measure pharma on PFS but rather QOL and my life right now is as good as it has ever been, infact BETTER. I say that because today I appreciate so much and I am grateful."

"I've had 4 infusions after pazopanib stopped working in March and I had 3 weeks without treatment. I've got my ct scan on Thursday morning and my 5th infusion after that with the results on Monday. I'm so pleased for X and sharing this news helps all of us."

"Back home yesterday and took my GSXR1000 out for a 3 hour ride. Life's just amazing right now and if nothing else, following years of TKI's, Opdivo nivolumab has given me my life back……. My personal opinion is that Opdivo Nivolumab should be immediately available for all cancer patients where experience shows that this is of benefit and I might add, having had private medical insurance initially during my cancer journey (now being a NHS patient) there is not that much difference in cost between Pazopanib, Axitinib and Nivolumab. However, my experience is that Nivolumab far exceeds the two prior systemic therapies and certainly in terms of energy and moral. Further, I know for a fact I would not have been able to undertake any work whilst on TKI's but definitely under Nivolumab. As a cancer patient…….. I am pleased to confirm that Opdivo Nivolumab has brought me back from the brink of death, able to regain my life."

'After a few problems last year …… the scans were showing that perhaps pazopanib had stopped working. Lymph nodes in my diaphragm and abdomen had increased. I came off that in March and was accepted on the Early Access Scheme for Nivolumab. I've had 4 infusions so far and the difference in the treatment is incredible. I've had no side effects and feel like my quality of life has improved immensely. My father passed away last year of the same cancer, so to have this drug available now for people like me has given me, my family and friends so much positivity and excitement about the future of cancer treatment."

"Axitinib has now stopped working as lymphs are appearing in his neck and lower back, causing a great deal of pain. We were desperate as only one drug was left and at the start of this journey, we were told that this drug was quality over quantity. Then we read about this new drug...if it works X could live for a few more years. I am very selfish; I don't want him to die anytime soon. My middle daughter gets married this year and we have a young Grandson. X has so much to live for, he worked full-time from the age of 16 till he was diagnosed in 2013 and paid fully into the national health system and I think he deserves the chance to live a bit longer. He is 48 so not an old man." This patient is now taking nivolumab via EAMS.

Thank you for allowing us to take part in this single technology appraisal. We welcome the opportunity to put forward the views of our Kidney Cancer Support Network patient community for this important health technology appraisal of nivolumab in advanced or metastatic renal cell carcinoma.

Best regards

[redacted]

Kidney Cancer Support Network

Web: www.kidneycancersupportnetwork.co.uk
Email: [redacted]

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Previously treated metastatic renal cell carcinoma is currently treated with either 2nd line axitinib or everolimus according to current NICE guidance. Both drugs have been proved to increase progression free survival (PFS) although the median PFS benefit for both is limited (4.8 month median PFS for axitinib and 4.0 months for everolimus). Both drugs have a manageable safety profile although most patients taking these agents do have some side effects from them. They are oral medicines.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

It was not possible to identify subgroups from the registration study that had a statistically different chance of benefiting from nivolumab.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Nivolumab should be given by cancer centres with experience of using immuno-oncology agents.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Nivolumab is approved for use in advanced melanoma and lung cancer.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no UK clinical guidelines currently that cover the use of nivolumab for renal cell carcinoma.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Nivolumab is given by i.v. infusion fortnightly. This schedule and administration route is familiar to cancer centres. Blood tests and CT scan assessments are as current standard care with axitinib or everolimus. The treatment is acceptable to patients.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Response assessment is usually by CT based imaging every 12 weeks. If there is evidence of radiological or clinical benefit treatment would generally continue for a further 12 week period until the next CT assessment. If there is no evidence of benefit treatment is discontinued. There are no biomarkers that allow identification of groups of patients who will or will not benefit from nivolumab treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Nivolumab represents a major breakthrough in the treatment of advanced renal cancer. Current standard of care with tyrosine kinase inhibitors (TKIs) and an mTOR inhibitor has significantly improved outcomes for these patients, however the duration of benefit with 2nd line and subsequent treatments is usually modest and limited for most patients. In comparison with everolimus, nivolumab significantly improved median overall survival by approximately 6 months (HR 0.73). It is premature to identify predictors of long term benefit but we know that this class of agents is associated with long term benefit in melanoma. The shape of the PFS curve in the RCC registration study implies that a plateau is developing with a group of patients having durable benefit. No doubt modelling will explore this further and planned later data analyses will provide data. The patient population in the study is directly applicable to the UK population and a number of UK patients benefited from being recruited into this clinical trial.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side effect profile of nivolumab, in comparison with many oncological agents in the palliative setting, is good. Quality of life data from the registration study has confirmed that patient experience and quality of life is significantly better on nivolumab than on everolimus. Cancer centres now have growing experience managing those patients who require side effect management from exposure to immune-oncology agents.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

<u>Implementation issues</u>

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place

**within
3 months, NICE may advise the Department of Health to vary this direction.**

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As the agent requires iv administration cancer centres will need to ensure that capacity for iv infusion is planned for. However the number of patients with advanced RCC receiving this treatment will be very much smaller than the lung cancer population receiving the same agent and it is therefore unlikely that the RCC patient population will significantly impact upon resourcing.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: James Larkin

Name of your organisation: The Royal Marsden Hospital

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

  an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

  other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

If available on the NHS Nivolumab will be the 2nd line treatment most often prescribed after failure of 1st line Sunitinib or Pazopanib. There are no major geographical variations or significant differences in opinion among experts. Axitinib is a current NICE approved alternative. For Nivolumab there are no well-established sub-groups that may get differential benefit and it will be prescribed by oncologists experienced in treating advanced RCC. No relevant guidelines.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Nivolumab is delivered intravenously in comparison with potential comparators Everolimus and Axitinib which are delivered orally. This has practical implications. Nivolumab is better tolerated than either Axitinib or Everolimus with important implications for quality of life. The CHECKMATE025 registration trial for Nivolumab was representative of patients with advanced RCC seen in UK routine practice. The most important outcome of the trial was prolongation of overall survival for Nivolumab in comparison with Everolimus.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Not applicable

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Nivolumab is delivered intravenously 2 weekly until disease progression so extra resources e.g. day unit and pharmacy will be needed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by the NCRI Bladder & Renal Cancer CSG-RCP-ACP-RCR and consequently I will not be submitting a personal statement.

Name: Dr Paul Nathan

Signed:

Date: 16/05/2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Nivolumab

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Jon Birchall
Name of your nominating organisation: Kidney Cancer Support Network
Do you know if your nominating organisation has submitted a statement?

☒ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☒ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☒ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?
-

☐ Yes ☒ No

Do you have experience of the treatment being appraised?

☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

Over the last three years I have been given a life expectancy varying between 6 months and ten years. Trying to live a normal life and, and come to terms with this prognosis is difficult, to say the least.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I want to cure the disease, as the alternative is not very appealing.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

So far I've has surgery (a radical nephrectomy) and high dose interleukin. The surgery was tolerable and the Interleukin, horrendous.

I was misdiagnosed in 2010, and this issue is one of the principle barriers standing in the way of improved survivability of the disease.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment

being appraised.

In certain cases Nivolumab appears to be highly effective, and in my case the side effects are fairly minimal. I am able to work and live a relatively normal life.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

The only other treatment I have used is high dose Interleukin. The side effects are horrendous and took a year to recover from

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

It is costly in financial and physical terms as we have to travel from Hereford to London every fortnight, for the treatment.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Anecdotally some patients seem to be coping much better with the drug than others

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Clearly more research needs to be done in identifying those patients who would most benefit from the treatment

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

N/A

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

From my knowledge there have been some spectacular improvements in certain patient's condition through use of the drug.

Is there anything else that you would like the Appraisal Committee to consider?

I would like to see the committee request further trials on the drug, in combination and sequence with other drugs to improve the effectiveness and possible curative properties.

For my part I intend to have Interleukin again, once my year on Nivolumab is ended. I know from my profession, that treatment of an organism with a single chemical only encourages the development of resistance in the organism.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Hope is the best medicine .Nivolumab gives hope

- The drug needs to be made widely available to find out where it best fits into the treatment of Kidney cancer.
- Cost is an issue, but many patients will never draw their pension. I feel they have made payments on account and are entitled to have the best quality of life, for the remainder of their life. Nivolumab appears to be effective, with minimal side effects in many cases.
- The drug needs to be trialled in combinations and sequences with other drugs.
- I would ask the manufactures of the drug to make a donation to my charity, which is helping to fund a research project, looking for biomarkers to aid early detection kidney cancer. It is possible that early detection would enable treatment with immuno therapies as opposed to surgery.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Alison Fielding
Name of your nominating organisation: Kidney Cancer Support Network
Do you know if your nominating organisation has submitted a statement?

☐ Yes

Do you wish to agree with your nominating organisation's statement?

☐ Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

 a patient with the condition?

Yes

 a carer of a patient with the condition?

No

 a patient organisation employee or volunteer?

Yes

Do you have experience of the treatment being appraised?

☐ Yes but not as a patient who is currently on the treatment. I work as a volunteer supporter to kidney cancer patients and have researched patient feedback on the treatment from across the world.

If you wrote the organisation submission and do not have anything to add, tick here (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with Stage 4 RCC in March 2014. I had been breathless and having declining heart and kidney function since 2011. This was attributed to dilated cardiomyopathy due to the size of my heart and when my heart function was down to 15%, after a 9 month administrative delay, I was sent for an assessment for a heart transplant. Scans as part of this process identified a 13cm tumour and spread to heart (4cm), adrenal gland, lymph nodes and lungs. I was accepted for high risk surgery and , after initial complications, have recovered well. Spread to my brain was identified in November 2014 and I underwent successful Stereotactic surgery in December. I had an internal cardiac defibrillator fitted in March 2015 prior to starting on Pazopanib. The Pazopanib has held the cancer in check so far with tolerable side effects (diarrhoea and hair changes.) I am now able to exercise, am largely self reliant and act as a chair of a national health charity. From sleeping everyday and extreme breathlessness, I would now rate my quality of life as 8/10.

Whilst I have been lucky so far, I have seen many patients die and suffer severe difficulties including paralysis. TKIs offer an important but sometimes fleeting window of stability. I have recently had a return of the sweats which heralded my initial diagnosis and the subsequent relapse. My fear is that it has ceased being responsive to Pazopanib.

My membership of several patient communities (Kidney Cancer Support Network, Smart Patients and a face to face group at Guy's Hospital) has highlighted to me the impact of a terminal diagnosis on the family as well as the patient. I have supported several families who have been at the end of current treatments and have had to watch their loved ones die. Many of these were young families. Sarcamotoid features on their cancer made treatment options limited and I believe this needs recognition as this new option is considered.

As someone with both a brain metastasis and heart problems, most clinical trails would seem to be closed to me. So I need access to licensed and commissioned drugs and to patient communities so that I can assess the real world impacts of new treatments.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

For most patients, I am sure that they would prioritise being no evidence of disease or the hope of this however clinically unlikely. Failing that shrinkage or stability.

For me, like many others, the day to day quality of my life is important. Pazopanib has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths which may cause pain or complications.

Although it is minor in the scheme of things, I find the changes to my appearance distressing. The white, thinning hair and different colour skin make me feel nearer to death and I don't recognise myself in the mirror. It also singles people out as ‘cancer patients’ and I know that men feel equally upset by it.

TKIs can also cause issues with thyroid, blood pressure and cholesterol. I take 10 different drugs everyday and would like a treatment with less need to have a cocktail of drugs at a cost to my body and the NHS budget.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I think surgery has the most proven impact on survival and QOL. I had an open procedure due to the involvement of my heart but would support more laparoscopic and robotic surgery as I have witnessed much easier recovery.

Current TKIs offer stability for many - sometimes for years. Those who I know on Pazopanib seem to have a more favourable side effect profile. Even though Axitinib patients are 2nd or 3rd line, I have met many with a reasonable quality of life and some of these have continued to work. I have met patients on Everolimus and it caused them a greater burden of side effects versus a smaller gain than other TKIs.

Stereotactic surgery on my brain metastases was quick and relatively painless. It has been effective after just a half day appointment and no neurological follow up. Other countries use this more widely for control of metastases elsewhere such as the lungs and I would welcome examination of this as an option for RCC.

4. What do you consider to be the advantages of the treatment being appraised?

Please list the benefits that you expect to gain from using the treatment being appraised.

Patients who have accessed the treatment either on the EAMS scheme here or worldwide report a significant reduction in their side effects from previous TKIs and a substantial improvement in their quality of life. Those people whom I have communicated with in countries who had had access to Nivolumab (Opdivo) for longer have reported being able to return to work or reduce the amount of care which they required.

Richard said, “Just passed my 9 year survival anniversary. The highlight has been my Nivo trial experience with treatment over the past two years. Twice a month and no side effects that I can discern. I have had a close to complete recovery with only one small tumour still remaining in the liver.”

Many patients who have been able to access the drug reported increased energy and ability to tolerate more exercise. Indeed a search of Nivolumab side effects on a patient website showed walking, cycling and hiking to be top mentioned words in the forum.

From a patient mental health point of view, knowing that you have stage 4 cancer but not being on treatment or knowing that there are possibly more effective treatments that you can't access is very difficult. Carers seem to find this even harder as they live with a guilt of not having done everything they can. Access to the treatment would enable patients and their families to know that they had tried their best and achieve better mental health outcomes. In today's world of online patient communities, patients are more aware of other peoples experiences including their deaths. I volunteered with 4 patients who were parents of young children.They were waiting for Nivolumab to be approved but only one of them got to start the drug and she was too ill by that point to see any benefit. This ripples out to others and destroys their hope and positivity. We are hoping for some UK success stories from the few months it was available here.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

It has a greater success rate than Everolimus, a low side effect profile and offers a chance of progression free survival and even total regression in some cases.

For patients that have been on TKIs and had bad side effects, this treatment could see a step change in quality of life. One patient said, "No GI issues at all like I had with Sutent. Some knee and shoulder pain, but I am used to that from arthritis. Food is great, energy is great... I feel cured!! I realise I am not... but I never knew I had kidney cancer until they told me I did... and I never was sick. Start Sutent, and that is all I felt... sick. The surgery to remove my kidney, took me about 8 or 10 months to feel good again... brain met surgery... easy... my hard part was the Sutent side effects."

Another patient said, "I have had three infusions of Nivolumab and I feel great. So far only minor SE. There was some shoulder, neck and headaches at first, but none in the past week after my last infusion. I was on Votrient for almost year and I am so glad to be rid of the GI side effects. My energy is

good, my taste buds are back, no more tingling in hands and feet and my hair colour is slowly returning.“

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Most patients view Nivolumab as a ‘wonder drug’ due to the media coverage and are impatient to be able to try it. I have read the original papers about the response rate and realise that it will not work for many people. Despite this,we are agreed that people should be able to access it and try it and have early reviews of how it is working for them.

5. What do you consider to be the disadvantages of the treatment being appraised?

The treatment is given intravenously every 2 weeks rather than the oral TKIs which only require a monthly hospital visit. Patients will typically be travelling some distance to a regional kidney cancer centre in order to access the drug.

For those patients who need to take time off work or have a partner travel with them to treatments, their hospital time would be increased.

Balanced against the extra travel and time is the lower side effect profile and enhanced quality of life. Most patients report that they feel much better able to cope with life and some have returned to work. Half a day in hospital is preferable to the same amount of time in the toilet due to TKIs or needing to sleep.

Some patients have reported shoulder pain and rashes and fatigue on the day of treatment. One had had inflammation of the prostrate and another had a temporary problem due to inflammation of a brain metastasis.

Please list any concerns you have about current NHS treatments in

England.

The only other non TKI treatment available is IL2. This is not suitable for many patients due to its toxicity and the need for patients to be in otherwise good health. Patients will apply to have this in the hope of being a complete responder. It is only available in a couple of centres and the costs to the NHS in in-patient care and the patient in travelling time and accommodation costs for family are high. I think it is an important facility to maintain but I think less people would try it as an early therapy if they could have Nivolumab.

Please list any concerns you have about the treatment being appraised.

None other than patients would benefit from more local provision for the chemo chairs whilst under the supervision of specialist centres.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not aware

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I think that clinicians should be able to prescribe Nivolumab as a first line treatment for patients with RCC with sarcomatoid features. Those I have known have had a poor response to TKIs so it seems a waste to try therapies that are unlikely to work. The disease progression is quick so special end of life rules should apply to give them access to another therapy.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I do not have enough evidence. The patients on the forum who have thrived have been those with the better performance status at therapy initiation.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

N/A

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Trials will typically review PFS and OS. OS is important to patients but so is their quality of life. One thing that strikes me from the experiences of those who have tried it is that their emotional and mental health seems to have improved. People are getting back to exercise, working and social engagements thereby improving their physical health and ability to live independently. Drug introduction trials led by manufacturers do not track the social impacts on patients and their carers. There is an opportunity for real-life research to track this following approval.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not aware.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Patients with rarer subtypes of Kidney Cancer such as those with Sarcomatoid features have fewer options and progress quicker than those with Clear Cell variants. Whilst I have no peer reviewed evidence, my

experience of assisting patients in this group has been that they were younger than the average RCC patient (30's and 40's.) All those that I visited/helped died within 12 months and had a poorer quality of life. 3 were wheel chair users as their cancer spread to their spine. Both they and their partners had had to give up work and needed community support.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

This offers the first opportunity for kidney cancer patients to benefit from advances in immunotherapy outside of a trial. Many patients such as myself can not access trials due to co-morbidities or having brain mets.

Is there anything else that you would like the Appraisal Committee to consider?

Recent trials are showing that patients who initially appear to have progression but who continue on treatment have a better overall survival than those who cease. It will be important to factor this into the prescribing rules given that the nature of the action of immunotherapy drugs will require a longer observation period.

SOURCE: http://bit.ly/1V8PVhU and http://bit.ly/1V8PDru JAMA Oncol 2016

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is an innovative treatment which shows greater chance of remission and substantial shrinkage
- Side effects are minimal leading to better quality of life
- Patients are willing to travel and take the extra time for treatment
- Patients and their carers will be more independent and economically productive.

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 15/69/20

BMJ Technology Assessment Group

Nivolumab for previously treated advanced or metastatic renal cell carcinoma

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

Authors: Steve Edwards, Head of Clinical & Economic Evidence, BMJ-TAG, London

George Osei-Assibey, Health Technology Assessment Analyst, BMJ-TAG, London

Andrea Berardi, Health Economics Manager, BMJ-TAG, London

Charlotta Karner, Health Technology Assessment Manager, BMJ-TAG, London

Fatima Salih, Health Economist, BMJ-TAG, London

Mariana Bacelar, Senior Health Economist, BMJ-TAG, London

Correspondence to: Steve Edwards, BMJ-TAG, BMJ Evidence Centre, BMJ Group, BMA House, Tavistock Square, London, WC1H 9JP.

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

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Contributions of authors:

Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the company's submission; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence
George Osei-Assibey	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Andrea Berardi	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the summary and economic sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the clinical sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic evidence; and drafted the summary and economic sections
Mariana Bacelar	Critical appraisal of the company's submission; and critical appraisal of the economic evidence

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology - Genitourinary
AUC	Area under the curve
BIC	Bayesian Information Criterion
BID	Twice daily
BMS	Bristol-Myers Squibb Pharmaceuticals Ltd
BNF	British National Formulary
BSC	Best supportive care
CC	Complication or comorbidity
CCC	California Cancer Consortium
CDF	Cancer Drugs Fund
CFB	Change from baseline
CHMP	Committee for Medical Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for review and Dissemination
CRPL	Castrate-resistant prostate cancer
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTC	Common terminology criteria
DC	Discontinuation
DMC	Data monitoring committee
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOL	End of life
EQ-5D	EuroQoL 5-dimension
ERG	Evidence Review Group
FKSI-15	15 Item Functional Assessment of Cancer Therapy Kidney Cancer Symptoms
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptoms – Disease-Related Symptoms

Abbreviation	In full
GCP	Good clinical practice
GI	Gastrointestinal
GP	General practitioner
HCHS	Hospital & community health services
HR	Hazard ratio
HRQoL, HRQL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic Renal Cell Carcinoma Database
INB	Incremental net benefit
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous or intravenously
IVRS	Interactive voice response system
KM	Kaplan Meier
LLN	Lower limit of normal
LY	Life year
LYG	Life year(s) gained
MEL	Melanoma
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mL	Millilitre
MSKCC	Memorial Sloane Kettering Cancer Centre
MTOR	Mammalian target of rapamycin
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	NON-small cell lung cancer
OD	Once daily
ONS	Office of National Statistics
OP	Outpatient
OR	Overall response or odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PC	Palliative care
PD	Progressive disease
PD-L1	Programmed death-ligand1
PD-L2	Programmed death-ligand2
PFS	Progression-free survival
PFSN	Progression-free survival off treatment
PFST	Progression-free survival on treatment

Abbreviation	In full
PH	Proportional hazards
PO	Proportional odds
PPS	Post-progression survival
PPSN	Post-progression free survival off treatment
PPST	Post-progression survival on treatment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QQ	Quantile-quantile (plot)
Q2W	Every two weeks
Q3W	Every 3 weeks
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
SAE	Serious adverse event
SD	Stable disease or standard deviation
SGA LoT	Subgroup analysis for line of therapy
SNP	Single nucleotide polymorphisms
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TC	Terminal care
TKI	Tyrosine kinase inhibitor
TEAE	Treatment-emergent adverse events
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation, time to discontinuation
TTP	Time-to-progression
Tx	Treatment
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel Lindau
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company, Bristol-Myers Squibb (BMS), submitted clinical and economic evidence in support of the effectiveness of nivolumab for previously treated patients with advanced/metastatic renal cell carcinoma (RCC), to the National Institute for Health and Care Excellence (NICE).

At the time of writing the Evidence Review Group's (ERG) report, nivolumab has not been granted marketing authorisation in England. According to the company, marketing authorisation application was submitted to the European Medicine Agency (EMA) in October 2015. In addition, the Committee for Medical Products for Human Use (CHMP) gave a positive opinion on nivolumab on 25th February 2016.

The direct clinical evidence presented in the company's submission (CS) is derived from CheckMate 025, a phase III multicentre open-label randomised controlled trial (RCT). CheckMate 025 compared nivolumab with everolimus in patients with histologically confirmed advanced/metastatic renal cell carcinoma (RCC) who have received one or two previous anti-angiogenic agents.

The final scope issued by NICE specified the population of interest to be people with previously treated advanced/metastatic RCC. The ERG's clinical experts consider the population in CheckMate 025 to be reflective of patients in English clinical practice. The ERG therefore considers the population in CheckMate 025 to be relevant to the decision problem.

The intervention in CheckMate 025 was nivolumab, a fully human monoclonal immunoglobulin antibody that stops the evasion of immune-mediated tumour destruction and stimulates the patient's own immune system to directly destroy cancer cells, resulting in destruction of the tumour through pre-existing, intrinsic processes. The comparators of interest in the final scope issued by NICE are axitinib, everolimus (not recommended by NICE but until November 2015 it was funded by the Cancer Drugs Fund [CDF]) and best supportive care (BSC). The ERG therefore considers the comparator in CheckMate 025 (everolimus) to be in line with the NICE final scope.

In addition, all clinically relevant outcomes as specified in the NICE final scope including overall survival (OS), progression-free survival (PFS), response rate, adverse effects of treatment, and health-related quality of life (HRQoL) were reported in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary objective of CheckMate 025 was to evaluate the safety and efficacy of nivolumab in comparison with everolimus in patients with advanced RCC previously treated with anti-angiogenic

agents. To be eligible for enrolment, patients had to be aged ≥18 years with histologically confirmed advanced/metastatic RCC with a clear-cell component; measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1; disease progression during or after the last treatment regimen and within 6 months before study enrolment; and Karnofsky performance status ≥70%.

Patients in CheckMate 025 were randomised (1:1) to either nivolumab 3 mg/kg intravenously (IV) every 2 weeks (n=410) or to everolimus administered orally at a daily dose of 10 mg (n=411). Disease assessment was performed every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment.

In CheckMate 025, overall survival (OS), defined as the time from randomisation to date of death, was significantly better in the nivolumab group compared with everolimus group (hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.57 to 0.93; p=0.002). Progression-free survival (PFS) was defined as the time from randomisation to first documented RECIST defined progression or death from any cause. Median PFS was not statistically significant between nivolumab (4.6 months, 95% CI: 3.7 to 5.4) and everolimus (4.4 months, 95% CI: 3.7 to 5.5) groups (HR 0.88, 95% CI: 0.75 to 1.03, p=0.11).

Objective response rate (ORR) in CheckMate 025 was defined as the number of patients with a complete or a partial response divided by the number of patients randomised. Investigator-assessed ORR using the RECIST criteria was significantly higher in the nivolumab (25%) compared with the everolimus group (5%) (odds ratio [OR] 5.98; 95% CI: 3.68 to 9.72; p<0.001). The ORR, with a confirmatory scan after ≥4 weeks (that is, confirmed ORR), was also significantly superior (p<0.001) in the nivolumab group (22%) compared with the everolimus group (4%).

Health-related quality of life (HRQoL) in CheckMate 025 (assessed using the FKSI-DRS) significantly improved in the nivolumab group compared with the everolimus group after the first year of treatment. In addition, a higher proportion of patients in the nivolumab group (55%) experienced meaningful improvement in FKSI-DRS (defined as ≥2 point increase) compared with 37% of patients in the everolimus group (p<0.001).

In CheckMate 025, more patients in the everolimus group than in the nivolumab group experienced at least one treatment-related adverse event (TRAE) (nivolumab 78.6% vs everolimus 87.9%), grade 3–4 TRAEs (nivolumab 19% vs everolimus 37%) and discontinuations due to TRAEs (nivolumab 7.6% vs everolimus 13.1%). Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥5% incidence in the nivolumab group were skin (37.2%), gastrointestinal (GI) (24.4%), renal

(17.5%) and hepatic (16%), while in the everolimus group they were GIs (31.2%), pulmonary (18.6%) and skin (44.6%).

While CheckMate 025 compares nivolumab with everolimus, there are no head-to-head trials that compare nivolumab with the other treatments listed in the NICE final scope (i.e. axitinib and best supportive care [BSC]). The company therefore conducted an NMA.

In the NMA using ITT results for OS, [redacted]. In the NMA using crossover-adjusted results for OS, [redacted]

In the NMA for PFS, [redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* six-state model in Microsoft Excel® to assess the cost-effectiveness of nivolumab compared to everolimus, axitinib and best supportive care (BSC). The six health states were progression-free survival on treatment (PFST), progression-free survival off treatment (PFSN), post-progression survival on treatment (PPST), post-progression survival off treatment (PPSN), terminal care (TC) and death.

All patients started in the PFST health state, and could only transition to death through the TC tunnel state, which they were assumed to occupy in the eight weeks leading to death. The time horizon was set to 30 years. Weekly cycles were used, and no half-cycle correction was applied due to the short cycle length. Costs and quality adjusted life-years (QALYs) accrued were discounted at a rate of 3.5%.

An area under the curve (AUC) approach was adopted in the economic model, modelling the proportions of patients in each health state based on parametric survival curves for each clinical outcome. Overall survival (OS) was used to determine how many patients were dead or alive; progression-free survival (PFS) to determine the proportions of alive patients who had progressed or not; and time-to-discontinuation (TTD) data were used to inform the number of patients who were on or off treatment. OS, PFS and TTD were analysed independently. The comparison between

nivolumab and everolimus was informed by parametric survival analyses of OS, PFS and TTD data from the CheckMate 025 trial. A network meta-analysis (NMA) was carried out to estimate the relative treatment effects on OS and PFS between nivolumab and axitinib, and nivolumab and best supportive care (BSC), as no head-to-head evidence was available for these two comparisons.

Based on the CheckMate 025 trial data, a generalised gamma model was selected to extrapolate OS for nivolumab and everolimus, as it predicted survival in a plausible manner according to clinical expert opinion. The relative effectiveness of everolimus and BSC was incorporated by applying the crossover-adjusted hazard ratios (HR) from the NMA to the OS curve of the everolimus arm in CheckMate 025, assuming BSC would be as effective as placebo.

The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit sufficiently well the data, and explored more flexible models. Spline-based survival models of Royston and Parmar were used to fit and extrapolated the CheckMate 025 PFS data. The PFS for axitinib and BSC was estimated by applying the HR estimated in the NMA to the everolimus curve, assuming that BSC was equally as effective as placebo.

The company used the same survival analysis approach to model TTD data for nivolumab and everolimus as for PFS, using spline-based models for nivolumab and everolimus. In the absence of TTD data for axitinib, the company assumed that treatment was continued until disease progression. As no treatment duration was associated to BSC, no assumption on TTD was necessary.

Pharmacological resource use for nivolumab, everolimus and axitinib was based on the treatment indications. The company assumed that the proportion of planned drug doses received observed in the trial would be applicable. The proportion of nivolumab and everolimus actually received by patients and thus assumed to be reimbursed by the NHS was based on data collected in the CheckMate 025 trial, and was equal to 92% and 94%, respectively. The proportion of planned axitinib received was 102%, based on the AXIS trial as reported in the single technology appraisal, "axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment" (TA 333). Patients were allowed to receive treatment after disease progression, in line with the clinical stopping rules of all the active interventions with the exception of axitinib, due to lack of TTD trial data.

Resource use in the progression-free and post-progression survival health states was assumed the same as that used in TA 333. Patients were assumed to require general practitioner (GP) visits once a month before and after progressing. They were also assumed to have monthly blood tests and a computerised tomography (CT) scan every 3 months before progression, 1.5 specialist palliative care nurse visits per month and to receive pain medication following disease progression. The cost of TC

was considered in the model, based on a paper by the King's Fund on improving choice at the end of life.

The company only included Serious Grade III/IV treatment-related adverse events (TRAEs) experienced by 1% or more of patients in either arm of the CheckMate 025 trial. These were pneumonitis, anaemia, diarrhoea and pneumonia. The rates and durations assumed for nivolumab and everolimus were based on the trial observations, and the management costs were applied weekly in the model. Due to lack of data, it was assumed that the total cost of management of TRAEs for axitinib was equal to that of everolimus. The weekly cost of management of TRAEs was £0.35 for nivolumab, and £1.31 for axitinib and everolimus.

The health-related quality of life (HRQoL) of patients receiving nivolumab and everolimus was estimated by analysing the EQ-5D data collected in the CheckMate 025 trial. A mixed effects model with fixed covariates for the effects of progression status, treatment allocation, and a variable for the interaction between treatment arm and progression status, with a random effect for subject was used. The health state utility values (HSUVs) for patients receiving axitinib was based on those used in TA 333, which were derived from the EQ-5D data collected in the AXIS trial. It was assumed that patients receiving BSC experienced the same quality of life as patients receiving axitinib. The HSUVs before progression were 0.80, 0.76, 0.69, and 0.69 for nivolumab, everolimus, axitinib and BSC, respectively. The PPS values were 0.73, 0.70, 0.61 and 0.61 for nivolumab, everolimus, axitinib and BSC, respectively.

The company's model results estimated an average survival benefit of 16, 11, and 24 (undiscounted) months for nivolumab compared to axitinib, everolimus and BSC, respectively. Nivolumab was expected to increase discounted quality-adjusted life-years (QALYs) by 1.07, 0.63 and 1.43 on average when compared to axitinib, everolimus and BSC, respectively. The company estimated pairwise incremental cost-effectiveness ratios (ICERs) of £42,417, £83,829 and £56,427 per QALY gained for nivolumab compared to axitinib, everolimus and BSC, respectively.

The deterministic sensitivity analysis showed that the base case results were sensitive to parameters and assumptions related to treatment effectiveness estimation and extrapolation. The probabilistic sensitivity analysis results for the comparison between nivolumab and axitinib, and nivolumab and BSC revealed substantial uncertainty surrounding the cost-effectiveness results and in particular the relative treatment effectiveness.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The ERG considers CheckMate 025 to be a well-designed and conducted trial, and is of the view that the trial is reflective of English clinical practice. In addition, safety and clinical efficacy results of CheckMate 025 are relevant to the decision problem as outlined in the NICE final scope for this STA.

Economic

The treatment effectiveness estimates for nivolumab and everolimus were based on data from a robust phase III randomised clinical trial. The methods used in the economic evaluation were clearly reported in the CS. The electronic model was transparent, sound, flexible and implemented efficiently. This allowed the ERG to make adjustments easily and carry out additional sensitivity analyses. The efficiency of the implementation allowed the ERG to carry out the analyses in a reasonable time.

The company used advanced methods to carry out statistical analysis in cases where standard methods were not deemed sufficient and when clinical expert opinion supported this choice.

1.4.2 Weaknesses and areas of uncertainty

Clinical

Axitinib is the only recommended treatment for second-line advanced/metastatic RCC by NICE in England. However, there is no direct RCT data comparing nivolumab with axitinib. Nivolumab was, therefore, compared with axitinib in the CS through an NMA. The ERG considers the results of the NMA to be unreliable for the comparison of nivolumab with axitinib. This is due to the network including trials with a range of different prior treatments, inconsistent use of adjustments for crossover for estimating OS, and use of immature OS data from one important link in the network. The results for axitinib were considered to lack face validity by the ERG's clinical experts and oncologists used by the company for clinical review.

Economic

The ERG considers that the most uncertain area in the CS was about the relative treatment effectiveness between nivolumab and axitinib, the only recommended treatment for second-line advanced or metastatic RCC. The company's base case presented relative treatment effects not considered plausible by the ERG's clinical experts and not expected by the oncologists interviewed by the company. In the ERG's opinion, the company failed to convey the substantial uncertainty associated to all the relative effectiveness estimates between everolimus and axitinib (i.e. intention-to-

treat OS HR, crossover-adjusted OS HR, PFS HR), [redacted]

The uncertainty associated to the relative treatment effects was further increased by the methodological issues found in the application of the HRs resulting from the NMA to non-proportional hazards survival models. This produced relative estimates considered unreliable by the ERG, in particular between nivolumab and axitinib, and nivolumab and BSC.

While a very comprehensive set of models were tested in the survival analyses, the ERG notes the company's lack of testing the assumptions of the different models. Given the uncertainty on the treatment effects, and the reliance of long-term estimates on the parametric models selected, the model assumptions should have been tested to assess the robustness of the OS, PFS and time-to-discontinuation (TTD) projections over the 30-year time horizon.

The company based the HSUVs for nivolumab and everolimus on the HRQoL observed in patients in the CheckMate 025 trial. However, the HSUVs for axitinib and BSC were based on the AXIS trial, with values substantially lower than the ones observed in the CheckMate 025 trial. The ERG is not satisfied with the company's justification of this difference. In particular, clinical experts considered completely unreasonable that the HRQoL patients progressed after receiving everolimus would be higher than the quality of life of patients not progressed after treatment with axitinib. The ERG's clinical experts agreed that, while the toxicity profiles would be different, the overall HRQoL between patients treated with axitinib or everolimus would be comparable, and that there was no rationale for a difference following treatment discontinuation between treatments.

The ERG identified two main issues with the company's assumptions about resource use and application of costs:

- The proportion of planned drug doses received by patients were not satisfactorily described and justified;

- Costs included subsequent therapies beyond second line, which are not currently recommended and reimbursed in England. Given that the costs are considered from an NHS and PSS perspective, these costs should have not been included.

Finally, the ERG identified several modelling errors, which however had a very limited impact on the company's base case model results. In particular, the ERG identified flaws in the integration of OS, PFS and TTD curves, resulting in negative proportions of patients in the health states or total proportions of patients in health states exceeding 100%. The model amendments resulted in increases

in the ICERs for the pairwise comparison of nivolumab to axitinib, everolimus and BSC of £692, £2,307 and £331 per QALY, respectively.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG corrected the errors identified in the company's economic model, and carried out scenario analyses to test the company's assumptions deemed implausible or not sufficiently explored. The ERG looked at the impact of alternative assumptions surrounding:

- Relative treatment effectiveness between axitinib and everolimus. The company's NMA results, showing everolimus to be superior to axitinib, were deemed clinically implausible by the ERG's experts. The ERG assumed an equal effectiveness profile for axitinib and everolimus in terms of OS and PFS;

- Parametric model selected for the extrapolation of OS. The ERG assessed the impact of using a log-logistic model to extrapolate OS data from the CheckMate 025 trial, as it showed the best relative fit to data among the parametric models tested. The company preferred using a generalised gamma model to incorporate the feedback received from clinical experts, who thought the log-logistic model would provide overly optimistic survival estimates for everolimus;

- Parametric model selected for the extrapolation of TTD. The company did not justify using a complex spline-based model when a simpler accelerated failure time (AFT) model would be appropriate. The ERG tested the impact of log-normal and generalised gamma models on the model results;

- Health-state utility values (HSUVs) associated to axitinib and BSC. The company used two different data sources for the treatment alternatives: the CheckMate 025 trial for nivolumab and everolimus, and the AXIS trial for axitinib and BSC. The two sets of value were different, with the axitinib HSUVs markedly lower than the ones associated to everolimus and nivolumab. As the difference was considered not sufficiently justified, and in line with the ERG's clinical expert feedback, the ERG tested a scenario using the same HSUVs for axitinib and BSC as for everolimus;

- Proportion of planned drug dose received for the estimation of treatment acquisition costs. The ERG carried out two scenario analyses related to the assumption on the proportion of drug received. In the first scenario, the delayed doses of nivolumab were included in the total doses received, and not deducted as in the company's base case analysis. In the second scenario, the ERG assumed that patients would receive all planned doses of nivolumab and

everolimus. This was because the estimations of the proportions of planned doses of everolimus received were unclearly reported, and no justification was provided for assuming a constant reduction of the quantity of drugs received over time;

- Subsequent therapy costs. The ERG explored a scenario analysis removing subsequent therapy costs in the model, as currently there are no approved and reimbursed third-line treatment options for advanced or metastatic RCC in England.

The ERG selected a set of assumptions and modelling approaches considered more reasonable and appropriate to provide results considered more reliable to inform the decision problem. Based on the revised company's model. The ERG's base case was based on the following assumptions:

- Equal effectiveness profile (i.e. OS and PFS) between axitinib and everolimus. This is because, according to clinical expert opinion, axitinib is considered at least equally as effective as everolimus. According to the clinical experts consulted by the ERG, the assumption of equal effectiveness between everolimus and axitinib might result in overestimating the relative benefits of nivolumab compared to axitinib;

- Equal health-related quality of life (HRQoL) profile between axitinib, BSC and everolimus. The clinical expert interviewed by the ERG disagreed with the company's assumption of a lower HRQoL associated to patients treated with axitinib in both pre- and post-progression compared to everolimus;

- Using a log-normal distribution for time-to-discontinuation instead of the spline-based model proposed by the company. The ERG considers the company's justification not sufficient and prefers using a simpler model which demonstrated to fit well the data;

- Assuming that patients receive all planned doses of everolimus and nivolumab. The ERG considers that the calculations for the planned doses received were not sufficiently clear, and that the company did not justify the assumption of a constant reduction in the quantity of drug used over time;

- No subsequent therapy costs, as currently there are no approved and reimbursed third-line treatment options for advanced or metastatic RCC in the UK.

The ERG's base case ICERs for nivolumab compared to axitinib, everolimus and BSC were £74,132, £91,989 and £61,317 per QALY, respectively. The ERG also explored an equally plausible scenario by using a generalised gamma model for TTD, estimating ICERs of £81,696, £96,107 and £64,869 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively.

The ERG highlights substantial uncertainty on the relative treatment effectiveness between everolimus and axitinib, and, by propagation, between nivolumab and axitinib. In particular, the ERG notes that the company did not analyse appropriately the adjustments made to the relative treatment effects because of the presence of treatment switching in the trials included in the NMA.

The ERG assumed equal effectiveness between everolimus and axitinib based on clinical opinion, as the base case estimates presented by the company were deemed implausible. As the ERG's clinical experts stated that axitinib would be at least as effective as everolimus, the ERG's base case results are likely to underestimate the effectiveness associated with axitinib. In conclusion, based on the assumptions made in the model and according to clinical expert opinion, the ICER for the comparison between nivolumab and axitinib might have been underestimated.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Sections 3.1 and 3.3 of the company's submission (CS) outline the key aspects of advanced/ metastatic renal cell carcinoma (RCC) including a disease overview, aetiology, course and prognosis, and prevalence and incidence.

Kidney cancer accounts for 3% of all new cancer cases and is the seventh most common cancer in the UK.[(1)] Two main types of kidney cancer are observed in adults, namely transitional cell cancer of the renal pelvis and RCC. In RCC, cancerous cells develop within the epithelia of the renal tubules. RCC is the most common type of kidney cancer, accounting for 80% of all kidney cancer cases diagnosed in the UK.[(1)] Histologically, RCC with a clear cell component accounts for 75% of all RCC cases.[(1-4)]

Smoking and obesity are the most common risk factors for RCC, contributing to about 42% of kidney cancers in the UK.[(1)] Other risk factors include hypertension, diabetes, renal failure, occupational exposure to toxic compounds such as asbestos, analgesic drug abuse, genetic conditions such as familial history of kidney cancer and Von Hippel Lindau (VHL).[(1, 5-10)] The incidence of kidney cancer in the UK is strongly related to age, with age-specific incidence rates rising sharply from around age 45-49, and peaking in the 85-89 age group. In the UK in 2011-2013, on average each year half (50%) of kidney cancer cases were diagnosed in people aged ≥70 years.[(1)] Men are up to twice more likely to develop RCC than women.[(1, 11, 12)]

The company's description of the disease burden of RCC is outlined in Box 1.

Box 1. Burden of disease of RCC (CS, pg 36, Section 3.1)

In the early stages of disease, RCC is relatively asymptomatic and often detected incidentally during medical investigation for other conditions.[(7)] When symptoms do occur, often as a result of disease progression, those classically observed include gross haematuria (blood in the urine), pain or discomfort in the upper abdomen or back (flank pain) and a palpable lump or mass in the kidney area; patients with metastatic disease may also present with symptoms due to metastases.[(1, 7)] The symptoms of advanced disease and the generally poor prognosis for patients with advanced RCC can also significantly impact individual patients' everyday lives and overall wellbeing.[(11, 13-15)] Patient HRQOL can also be further reduced as a result of significant toxicities related to treatment for advanced RCC. In addition to patient burden, advanced/metastatic RCC can also present significant burden to informal caregivers and wider society, primarily as a result of direct care requirements and reduced life expectancy; both of which are worsened with disease progression.[(11, 16-18)]
Abbreviations in box: CS, company submission; HRQoL, health related quality of life; RCC, renal cell carcinoma

RCC is divided into stages (CS, pg 35, Section 3.1) using the American Joint Committee on Cancer (AJCC) system which classifies the size of the tumour, the involvement of the lymph nodes and the presence of distant metastases. Stage I RCC (localised RCC), which is confined to the kidney, is potentially curable with surgical resection, and about 90% of patients with stage I RCC will survive for at least 5 years.[19] Advanced/metastatic RCC (stages III and IV), which is the focus of this STA, has a poorer outlook with 5-year survival rate of 10–15%.[19] In the advanced stage of RCC, the cancer cells have spread to a lymph node (advanced RCC) or to tissues around the kidney and may have spread to other organs in the body (metastatic RCC).[1]

The company's account of the scoring systems for prognosis in patients with advanced/metastatic RCC is presented in Box 2.

Box 2. Scoring systems used in prognosis in advanced/metastatic RCC (CS, pg, 35, Section 3.1)

The two main scoring systems used to assess prognosis in advanced/metastatic RCC: MSKCC score and a slightly modified version, known as IMDC or Heng criteria.[7] In the MSKCC scoring system, the presence of five criteria (Karnofsky performance status <80%; haemoglobin < LLN; time from diagnosis to systemic treatment of <1 year; corrected calcium > ULN lactate dehydrogenase > 1.5 times ULN are added up (one point for each criteria) to categorise the patient into favourable (no points), intermediate (1-2 points) and poor risk (3-5 points) groups, which are associated with worsening predicted survival.[7] Of specific interest in consideration of the nivolumab mechanism of action (see Section 2.1), some studies have also suggested that PD-L1 expression in RCC is associated with a poor prognosis, presumably because of its immunosuppressive function.[20-22]

Abbreviations in box: CS, company submission; LLN, lower limit of normal; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloane Kettering Cancer Centre; PD-L1, programmed death ligand-1; RCC, renal cell carcinoma; ULN, upper limit of normal

Overall the evidence presented in the submission is in line with the health problem as outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE).[23]

2.2 Critique of company's overview of current service provision

According to the CS (pg 43–44, Section 3.3) there were 8,505 kidney cancer cases in England in 2013,[24] and the average annual increase in incidence from 2005 to 2013 was 6%.[25] Using the 6% annual increase in incidence, the company projects the incidence of kidney cancer in England in 2016 to be 10,130. Based on data which suggest 80% of all kidney cases are RCC,[26, 27] and that 30% of all RCC cases are advanced disease,[3, 27-30] the company predicts the incidence of advanced/metastatic RCC in England for 2016 to be 2,431. In addition, based on estimates that about 75% of all diagnosed advanced/metastatic RCC cases in UK are treated with systemic therapy at first-line,[31, 32] the company estimates that there will be 1,823 patients with advanced/metastatic RCC in England who

have received at least one prior therapy. The ERG's clinical experts consider the estimates provided by the company in the CS to be reasonable.

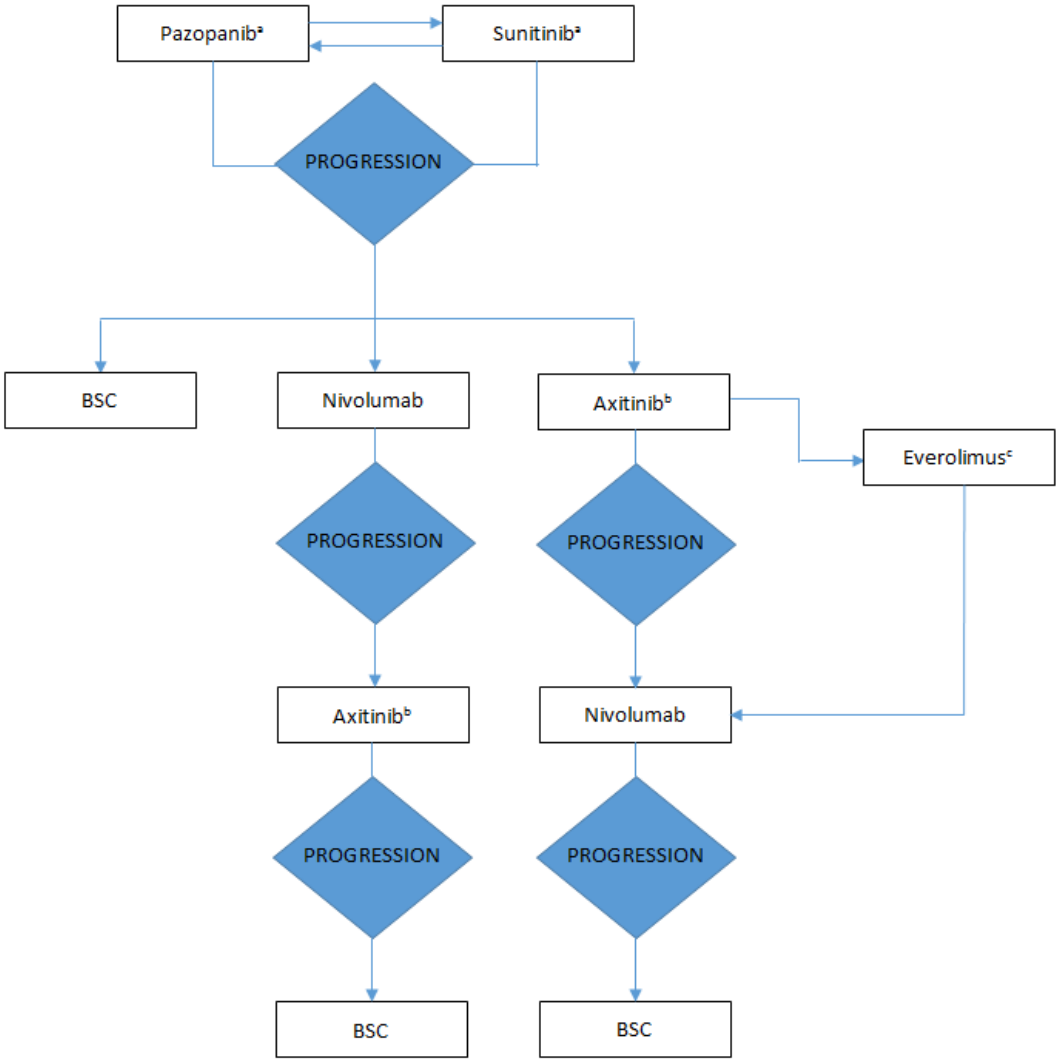
Section 3.5 of the CS (pg 35) states that "In the absence of a cure for advanced RCC, goals of treatment are to extend life and delay disease progression while relieving physical symptoms and maintaining physical function. Due to restricted treatment choice and limitations with treatments that are available, these goals are not being met for many patients with advanced RCC who have received prior therapy".

Currently first-line treatment options recommended by NICE are pazopanib[33] and sunitinib[34], both tyrosine kinase inhibitors (TKIs), and axitinib[35] (TKI) for second-line therapy. In England until November 2015, everolimus (mammalian target of rapamycin [MTOR]) was also available through the Cancer Drug Fund (CDF) in patients who have had prior treatment with only one TKI and are contraindicated to second-line axitinib therapy or show excessive toxicity to axitinib within three months of treatment initiation and have no evidence of disease progression.

However, neither axitinib nor everolimus have a proven overall survival (OS) benefit for patients with advanced/metastatic RCC who have received prior therapy. The only phase III trial with axitinib showed no OS benefit compared with sorafenib in the second-line setting.[36] Prior to CheckMate 025[37], the only phase III trial with everolimus showed no OS benefit compared with best supportive care (BSC).[38]

In the CS (Figure 5, Section 3.2), the company presents a treatment pathway for patients with advanced/metastatic RCC in England based on NICE guidance, and the likely place of nivolumab in the pathway. As axitinib is the only recommended treatment for second-line advanced/metastatic RCC in England, it is the most relevant comparator.

Figure 1. Future clinical pathway of care for advanced RCC in England (CS, pg 42, Figure 5, Section 3.2)



Abbreviations in figure: BSC, best supportive care.
Notes: [a], patients who have not progressed and do not tolerate first-line pazopanib can switch to sunitinib and vice versa; [b], routinely funded only for patients who receive sunitinib at first line; [c] patients may receive everolimus only if they are contraindicated to axitinib or have excessive toxicity to axitinib and discontinue treatment within 3 months.

According to the CS (Sections 3.2 and 3.5) in advanced/metastatic RCC, nivolumab, which is an immunotherapy, offers interruption to the current sequential treatment using TKI followed by another TKI or TKI followed by MTOR or BSC, thereby reducing the risk of resistance and excessive overlap of similar adverse events between first- and second-line treatments. In addition, nivolumab may offer an active treatment option for patients who have exhausted all treatment options available in current clinical practice.

Section 2.4 of the CS outlines changes in current service provision and the likely impact of introducing nivolumab in second-line treatment of advanced/metastatic RCC. According to the CS (pg 31-32, Section 2.4) "Nivolumab is not a targeted therapy, and as such, additional tests or

investigations outside of those required for the diagnosis of advanced RCC are not needed. Nivolumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of nivolumab would utilise this existing National Health Service (NHS) infrastructure, although there may be a need for additional infrastructure/resource to accommodate regular intravenous (IV) administration in some units given current treatment options are oral in nature".

The ERG's clinical experts were of the view that, given resources are already stretched; the introduction of nivolumab into the clinical pathway may overwhelm the current intravenous infusion service provision.

The ERG agrees with the company that there is an unmet medical need for a second-line treatment option that is tolerable and with proven OS in advanced/metastatic RCC, but the ERG is also concerned that the introduction of nivolumab has the potential to overwhelm the current intravenous infusion service delivery.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company tabulated a summary of the decision problem and a comparison with the final scope issued by NICE[23], presented in Table 1.

Table 1. Summary of decision problem as outlined in the CS (Reproduced from CS Table 1, pg 16)

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	People with previously treated advanced or metastatic renal cell carcinoma	People with previously treated advanced or metastatic renal cell carcinoma	-
Intervention	Nivolumab	Nivolumab	-
Comparator(s)	Axitinib Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) Best supportive care	Axitinib Everolimus (not recommended by NICE but funded by the Cancer Drugs Fund) Best supportive care	Axitinib is the most relevant comparator for nivolumab in English clinical practice and is therefore presented as the key comparison in this submission. Comparisons to everolimus and best supportive care are also included in accordance with the specified scope of the decision problem
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 30 years is used in the base case analysis. Costs are considered from a National Health Service and Personal Social Services perspective. List prices are used within the submission document as requested by NICE.	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	None specified.	None specified.	-
Special considerations including issues related to equity or equality	If the evidence allows the following subgroups will be considered. These include: Previous treatment Prognostic score (for example, ECOG or Motzer) Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	None identified	-

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; NICE, National Institute for Health and Care Excellence

3.1 Population

The population described in this submission is the same as that defined in the final scope issued by NICE[23], that is, "People with previously treated advanced or metastatic renal cell carcinoma". In addition, the pivotal randomised controlled trial (RCT), CheckMate 025, [37] that provided the clinical effectiveness and safety data in the CS enrolled patients with advanced clear cell renal carcinoma for which they had received previous treatment with one or two regimens of anti-angiogenic therapy.

CheckMate 025[37, 39] also specified a Karnofsky performance status (PS) of ≥70% as an entry criteria. The ERG considers the trial populations to be largely in line with the NICE final scope,[23] although the scope did not specify patients with a specific performance status. In addition, the ERG's clinical experts consider participants in CheckMate 025[37, 39] adequately reflect English clinical practice post first-line therapy for advanced RCC.

3.2 Intervention

The intervention named in the NICE final scope is nivolumab, and the CS describes its pharmacological specification (Box 3).

Box 3. Description of the intervention (CS, pg 26, Section 2.1)

PD-1 is an immune-system checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy. Tumour cells can exploit this pathway by up-regulating

proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.
Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2. Nivolumab stops the evasion of immune-mediated tumour destruction and stimulates the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes.

Abbreviations in box: PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2

Nivolumab does not currently have a UK marketing authorisation for the treatment of advanced RCC. However, in November 2015 nivolumab received marketing authorisation in the US for treatment of advanced RCC in patients who have received prior anti-angiogenic therapy. Nivolumab has also been granted marketing authorisation by the FDA and the EMA for use in North America and Europe, respectively, for the treatment of advanced melanoma in adults, and for the treatment of squamous non-small cell lung cancer after previous chemotherapy in adults.

On 25^{h} February 2016, the committee for Medical Products for Human Use (CHMP) gave a positive opinion on nivolumab recommending extending the use of nivolumab to include the treatment of adult patients with advanced RCC who have received prior therapy

The pivotal RCT (CheckMate 025)[37] in the CS compared nivolumab with everolimus. Nivolumab was administered at a dose of 3 mg/kg of body weight as a 60-minute intravenous infusion every two weeks in line with the expected marketing authorisation.

3.3 Comparators

The comparators of interest in the final scope issued by NICE are axitinib, everolimus (not recommended by NICE, but until November 2015 it was funded by CDF) and best supportive care (BSC). Although BSC was not defined in the NICE final scope[23], according to the ERG's clinical experts it includes palliative radiotherapy, steroids (for bone pain and improve well-being), opioids (for pain control), antibiotics (for chest infection), bisphosphonates for hypercalcaemia and bone progression.

Currently axitinib is the only recommended second-line treatment option in England[35] apart from BSC, and therefore is the most relevant comparator for nivolumab in England. However, the ERG notes that the comparator in the pivotal trial in the evidence submitted by the company is everolimus. The company's justification for choosing this comparator was that at the time of initiation of the trial[37] everolimus was the only active treatment with market authorisation for patients with advanced RCC who had received prior therapy. There is no head-to-head trial comparing nivolumab to axitinib

or BSC in this population, therefore comparative efficacy has been estimated using indirect treatment comparisons. This is discussed further in Section 4 of this report.

3.4 Outcomes

The outcome measures listed in the NICE final scope[23] are:

- Overall survival (OS);
- Progression-free survival (PFS);
- Response rate;
- Adverse effects of treatment;
- Health-related quality of life (HRQoL).

These outcomes are all reported in CheckMate 025[37] that provided clinical efficacy and safety data for this submission.

In CheckMate 025,[37] the Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) consisting of nine specific questions that address lack of energy, pain, weight loss, bone pain, dyspnoea, cough, fevers and haematuria[40], was used to measure the symptoms of advanced/metastatic RCC. Each item/symptom on FKSI-DRS is rated using a Likert-type scale ranging from 0 (not at all) to 4 (very much). The total score is obtained by multiplying individual item scores by the number of items in the subscale, and dividing by the number of items answered. Total scores range from 0 (worst possible score) to 36 (best possible score). In addition, EQ-5D which is a generic HRQoL outcome measurement tool and the preferred for eliciting health-related outcomes[41] was used in CheckMate 025.[37] The ERG believes the FKSI-DRS and EQ-5D are valid and reliable measures of changes in symptoms of advanced/metastatic RCC that capture patients' HRQoL.

The company provided (CS, pg 115–122, Section 4.12) safety data of nivolumab compared with everolimus in the CheckMate 025.[37] This include summary safety data for all treated patients (CS, pg 117, Table 23), summary of treatment-related adverse events (TRAEs) with ≥10% incidence (CS, pg 119, Table 24), and summary of selected adverse events (AEs) reported up to 30 days after last dose (CS, pg 121, Table 25).

In summary the ERG considers the outcomes presented in the CS to be consistent with the NICE final scope.[23]

3.5 Other relevant factors

In the CS the company states, "No equality issues related to the use of nivolumab have been identified or are foreseen" (CS, pg 47, Section 3.6). The ERG agrees with this view.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

In the CS (pg 48, Section 4.1), the company describes the search strategy used to identify the evidence for the effectiveness of nivolumab and relevant comparators in the management of previously treated advanced or metastatic RCC. The search terms used for electronic database searches are presented in Appendix 2 of the CS.

Electronic databases (Embase, MEDLINE, Cochrane CENTRAL and MEDLINE-in-process) were searched on 24th November 2014 and the searches were not updated before the company made the submission. According to the company, it was not possible to complete an update due to the absence of a standard STA timescale. At clarification stage, the company informed the ERG that an update had been conducted on January 1, 2016 and two further RCTs were identified: the METEOR trial investigating the comparative efficacy of cabozantinib and everolimus[42]; and a California Cancer Consortium (CCC) trial investigating the comparative efficacy of TRC105 plus bevacizumab and bevacizumab monotherapy.[43] However, the inclusion of these trials would not have influenced the estimates of comparative efficacy in the network meta-analysis (NMA), which is discussed in Section 4.4.

Conference proceedings (American Society of Clinical Oncology [ASCO]; ASCO-Genitourinary [ASCO-GU] Symposium; European Society for Medical Oncology [ESMO], from 2012 to 2015), reference lists of relevant systematic reviews and meta-analyses, and unpublished data held by the company, were searched for additional studies of relevance to the decision problem.

The ERG notes that it was not mentioned in the CS whether the company supplemented the electronic database searches with searches in clinical trial registries (clinicaltrials.gov, clinicaltrialsregister.eu; etc.).

The ERG considers the search strategy used by the company to be appropriate. It included terms for population, intervention, comparators, and study design. However the ERG notes that the search strategy contained comparators not mentioned in NICE final scope.[23]

4.1.2 Inclusion criteria

The eligibility criteria of the systematic review of evidence are summarised in

Table 2.

Table 2. Eligibility criteria used in the search (reproduced from CS, pg 49-50, Table 6)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced RCC Previously treated patients	Patients with localised RCC Paediatric RCC patients Patients with non-RCC disease Treatment naïve patients
Intervention	Bevacizumab + α-interferon α-interferon Interleukin-2 Everolimus Temsirolimus Sorafenib Sunitinib Pazopanib Axitinib Cediranib Cabozantinib Nivolumab Nafatumomab IMA901 BNC105P Dalantercept TRC105P GDC-0980	Any other
Comparator	Any treatment from the above included list of interventions Placebo Best supportive care	None
Outcomes	Overall survival Progression-free survival Response rate Duration of response Time to progression Quality of life Safety and tolerability	None
Study design	Randomised controlled trials Systematic reviews/meta-analyses[a]	Non-randomised controlled trials Single-arm trials Observational studies Database analyses Pooled data analyses Non-systematic reviews *In-vitro* studies Preclinical studies Case reports/series Commentaries/letters/editorials
Language restrictions	English language only	None

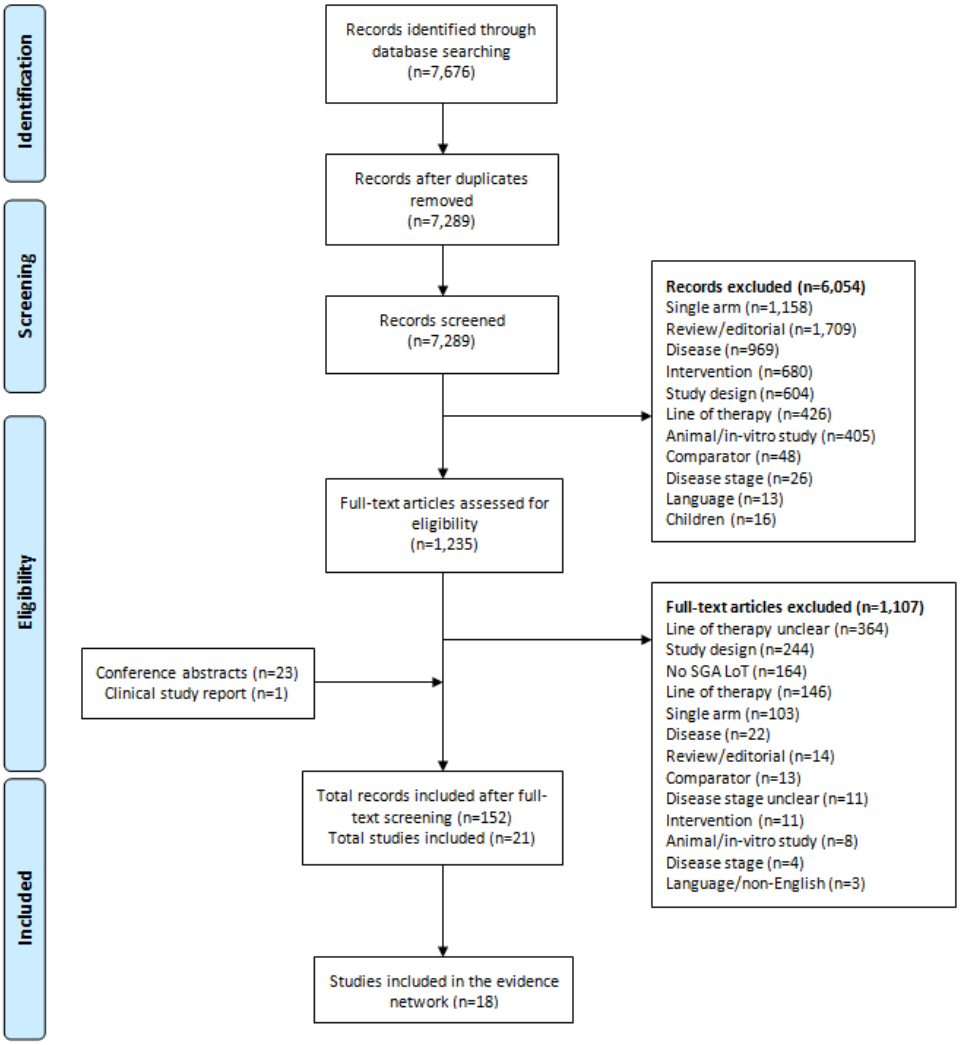
Abbreviation in table: RCC, renal cell carcinoma.
Notes: [a]included for reference review only

As mentioned previously, the ERG notes that the company included comparators outside the NICE final scope.[23] The company's reason was that it was based on a global search and was not limited to this STA. The ERG considers this appropriate as it facilitated the development of a complete network

for the indirect comparison. However, the ERG considers that relevant studies may have been missed due to the exclusion of non-English language trials.

The methods used to identify relevant studies during screening of abstracts for inclusion are in line with those recommended by the Centre for Reviews and Dissemination (CRD).[44] According to the CS (pg 50–51, Section 4.1), two reviewers independently assessed each reference (title and abstract) based on the eligibility criteria with disagreements between the two resolved by a third party. In addition, where multiple publications from the same trial were identified, all were included in the final list of articles meeting the eligibility criteria. A flow diagram of the number of included and excluded studies at each stage is captured in the Figure 2. Out of a total of 152 records included after full text review, 21 RCTs met the inclusion criteria, and 18 studies were included in the evidence network.

Figure 2. PRISMA flow diagram of the literature search process (reproduced from CS, pg 51, Figure 6, Section 4.1)



However, nine studies were included in the final NMA. The company's states the "The primary reason for study exclusion from the NMA was small sample size and/or limited data availability due to study results only being available from conference abstracts at the time of assessment".

Table 3 shows the RCTs identified in the systematic review search, and RCTs excluded in the final NMA with reasons. The ERG does not consider a small sample size alone to be a valid criterion for excluding trials from an NMA.

Table 3. RCTs included in the systematic review and final NMA (adapted from CS, pg 53 [Table 7] and pg 85 [Table 15])

Trial name	Treatment arms	Primary data source	Outcome
AXIS	Axitinib vs sorafenib	Rini *et al*. 2011[45]	Included in NMA: OS, PFS
CheckMate 025	Nivolumab vs everolimus	CheckMate 025 CSR[a(37, 39)]	Included in NMA: OS, PFS
DISRUPTOR-1	Everolimus plus BNC105P vs everolimus	Pal *et al*. 2015[46]	Not included due to limited data availability
ESPN	Everolimus vs sunitinib	Tannir *et al*. 2014[47]	Not included due to non-clear cell patients, small sample size and limited data availability
GOLD	Dovitinib vs sorafenib	Motzer *et al*. 2014[48]	Included in NMA: OS, PFS
Guo *et al.* 2015	Bevacizumab vs sorafenib	Guo *et al*. 2015[49]	Not included due to small sample size and limited data availability
INTORSECT	Temsirolimus vs sorafenib	Hutson *et al*. 2014[50]	Included in NMA: OS, PFS
Motzer *et al*. 2015	Lenvatinib plus everolimus vs lenvatinib vs everolimus	Motzer *et al*. 2015[51]	Not included due to limited data availability
Powles *et al*. 2014	Apitolisib vs everolimus	Powles *et al*. 2014[52]	Not included due to small sample size and limited data availability
Qin *et al*. 2012	Axitinib vs sorafenib	Qin *et al*. 2012[53]	Not included due to limited data availability
Ratain *et al*. 2006	Sorafenib vs placebo	Ratain *et al*. 2006[54]	Not included due to small sample size
RECORD-1	Everolimus plus BSC vs placebo plus BSC	Motzer *et al*. 2008[55]	Included in NMA: OS, PFS
RECORD-3	Everolimus vs sunitinib	Motzer *et al*. 2014[56]	Not included due to sequential trial design
SWITCH	Sunitinib vs sorafenib	Eichelberg *et al*. 2014[57]	Not included due to limited data availability
TARGET	Sorafenib vs placebo	Escudier *et al*. 2007[58]	Included in NMA: OS, PFS
TIVO-1	Tivozanib vs sorafenib	Motzer *et al*. 2013[59]	Included in NMA: PFS (not included in OS NMA due to trial crossover and limited information on how this was handled
VEG105192	Pazopanib vs placebo	Sternberg *et al*. 2010[60]	Included in NMA: OS, PFS
Yang *et al*. 2003	Bevacizumab 10mg vs bevacizumab 3mg vs placebo	Yang *et al*. 2003[61]	Included in NMA: OS, PFS
CRECY	Interleukin-2 vs interleukin-alfa-2a	Escudier *et al.* 1999[62]	Not connected to evidence network
Patel *et al.* 2008	Interleukin-2 plus SRL172	Patel *et al.* 2008[63]	Not connected to evidence

Trial name	Treatment arms	Primary data source	Outcome
	vs interleukin-2		network
Walter *et al.* 2012	IMA901 plus GM-CSF plus cyclophosphamide vs IMA901 plus GM-CSF	Walter *et al.* 2012[64]	Not connected to evidence network

Abbreviations in table: BSC, best supportive care; CSR, clinical study report; OS, overall survival; PFS, progression-free survival
Notes: [a]published since the time of review

In the PRISMA flow diagram (Figure 2), 364 full-text articles and 11 full-text articles were excluded on the basis of unclear line of therapy and unclear disease stage, respectively. There is no mention in the CS whether the company sought clarifications from the authors.

The company also identified one randomised dose- ranging trial (CheckMate 010[65]) and one non-randomised dose escalation trial (CheckMate 003[66]) from its internal clinical trial database to supplement the RCT data in the use of nivolumab in advanced RCC.

4.1.3 Critique of data extraction

Data extraction for each included study was independently undertaken by two reviewers, with any discrepancies between them resolved by a third party (CS, pg 53, Section 4.1). The ERG considers the method of data extraction employed by the company as the gold standard. The company provided a summary of trial methods including trial design, population, sample size, treatment arms, primary endpoint, and patient eligibility, outcomes, subgroups, and a description of the statistical methods of included trials (CS, pg 81–99, Section 4.10, Appendix 4).

4.1.4 Quality assessment

The company conducted an assessment of trial quality for studies that provided direct (CS, pg 67, Table 12, Section 4.6) and indirect evidence (CS, pg 99–102, Section 4.10, Table 13 and Appendix 4) using an adapted version of NICE's checklist for assessment of bias in RCTs.[67] A summary of the company's and the ERG's quality assessment of CheckMate 025[37, 39] is presented in Table 4.

Quality assessment of nivolumab trials

The ERG considers the company's approach to quality assessment of CheckMate 025[37, 39] as appropriate and meets standard practice of quality assessment of RCTs. In CheckMate 025, randomisation and allocation concealment were carried out using appropriate methods, and treatment groups were similar at baseline without any imbalance in drop-outs. In addition, analysis was based on intention-to-treat (ITT), however, the trial was open label. The ERG independently validated the quality of CheckMate 025, and agrees with that of the company.

Table 4. Quality assessment of CheckMate 025 (Adapted from CS, pg 67, Table 12)

	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Yes	Yes, randomisation was through an IVRS and stratified by MSKCC risk group, and number of prior anti-angiogenic therapies in the advanced or metastatic setting
Was the concealment of treatment allocation adequate?	Yes	Yes, the IVRS ensures concealment of treatment allocation since it is based on remote patient randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes, baseline characteristics were balanced between the two groups with no key differences between them.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No, the trial is described as open label.
Were there any unexpected imbalances in drop-outs between groups?	No	No, 339/410 (82.7%) patients discontinued nivolumab treatment and 369/411 (89.8%) discontinued everolimus treatment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No, all outcome measures were pre-specified in the CS (pgs 57-58, Section 4.3) and the CSR
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes. Standard censoring methods were used to take account of missing data in primary OS analysis and secondary PFS analysis.
How closely do the RCT(s) reflect routine clinical practice	Population, treatment arms, administration and outcomes all relevant to clinical practice in NHS England	The ERG's clinical experts consider participants in CheckMate 025 adequately reflect English clinical practice post first-line therapy for advanced RCC

Abbreviations in table: IVRS, interactive voice response system; MSKCC, Memorial Sloan Kettering Cancer Centre; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Quality assessment of CheckMate 010 and CheckMate 003 were conducted by assessing risk of common types of bias as well as the applicability of study results to the decision problem (CS, pg 78–79, Section 4.11, Tables 6 and 7, Appendix 4). The risk of bias was low on selection bias, whether patients reflect UK clinical practice, whether all patients were accounted for, whether the analysis included ITT, whether results have both internal validity, and whether findings are internally and externally valid. The ERG validated the company's assessment of CheckMate 010 and CheckMate 003 and agrees with the company. The company's and the ERG's assessment of CheckMate 010 and CheckMate 003 are shown in Appendix 10.1.

Quality assessment of trials included in the NMA

The company critically assessed the quality of all the 9 trials included in the final NMA using the Jadad scale[68] (CS, pg 99, Table 13, Appendix 2), which is a quantitative measure of study quality. The scale is from 0 (bad/poor quality) to a maximum of 5 (good quality). The Jadad scale has been criticised due to its weakness in assessing the quality of RCTs.[69] It includes only 3 items:

randomisation, blinding, and withdrawal. However, the company supplemented the Jadad scale with an assessment of all items including in the NICE RCT checklist: allocation concealment, baseline characteristics, outcome selection and reporting, and statistical analysis. Of the nine trials informing the NMA had appropriate randomisation and allocation concealment procedures, and in four trials this was not adequately described. Baseline characteristics were well balanced in all trials, however, only four of the trials were double blind with the remaining five being open label. The company's assessment of RCTs included in the NMA is shown in Appendix 10.1.

4.1.5 Summary of review methods

The search for relevant RCTs was comprehensive and systematic, although it included several comparators outside of the NICE scope. However, this may have facilitated the creation of a complete network. The inclusion of trials was in line with the scope, however, the company excluded non-English language references and trials with a small sample size. In addition, some studies were excluded due to unclear line of therapy and unclear disease stage. As a result, the ERG is concerned that relevant studies may have been missed. The quality assessments of the included trials seem to have been done in accordance to standard criteria recommended by NICE.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The company's systematic review of RCTs identified one trial[37, 39] comparing nivolumab with everolimus in patients with advanced clear-cell RCC who have been pre-treated with one or two regimens of anti-angiogenic therapy. According to the CS (pg 106, Section 4.11), the company did not conduct a systematic review to identify non-RCT evidence since RCT data are available for all comparators relevant for the decision problem. However, the company identified one randomised dose- ranging trial (CheckMate 010[65]) and one non-randomised dose escalation trial (CheckMate 003[66]) from its internal clinical trial database to supplement the RCT data in the use of nivolumab in advanced RCC.

Table 5 is a summary of CheckMate 025, CheckMate 010 and CheckMate 003. In the CS (pg 22, Section 1.3), the justifications for inclusion of CheckMate 010 and CheckMate 003 was to provide supportive long term survival data (3 years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab.

Table 5. List of relevant RCTs and non-RCTs (adapted from CS, Table 8, pg 54 and Table 19, pg 106)

Trial name (NCT number)	Objective	Intervention	Comparator	Primary study reference
CheckMate 025 (NCT01668784)	To compare nivolumab with everolimus in	Nivolumab 3mg/kg IV every two weeks	Everolimus 10mg orally every day	Motzer *et al*. 2015[37]

Trial name (NCT number)	Objective	Intervention	Comparator	Primary study reference
	patients with RCC who had received previous treatment			
CheckMate 010 (NCT01354431)	To evaluate whether a dose-response relationship exists for nivolumab	Nivolumab 0.3, 2 or 10mg/kg IV Q3W	-	Motzer *et al*. 2015[65]
CheckMate 003 (NCT0730639)	To evaluate the safety, antitumor activity and pharmaco-kinetics of nivolumab	Nivolumab 1, 3 or 10mg/kg IV Q2W	-	McDermott *et al*. 2015[66]
Abbreviations in table: IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma				

4.2.1 Trial conduct

CheckMate 025[37, 39] is an open-label, phase III trial conducted in 146 sites in 24 different countries. The study was initiated in October 2012 and data presented in the CS are based on a clinical database lock of 18th June 2015. A total of 1,054 patients were recruited and 821 were randomised. The main eligibility criteria of CheckMate 025 are presented in Table 6.

Table 6. Eligibility criteria of CheckMate 025 (adapted from CS, pg 56-57, Table 9)

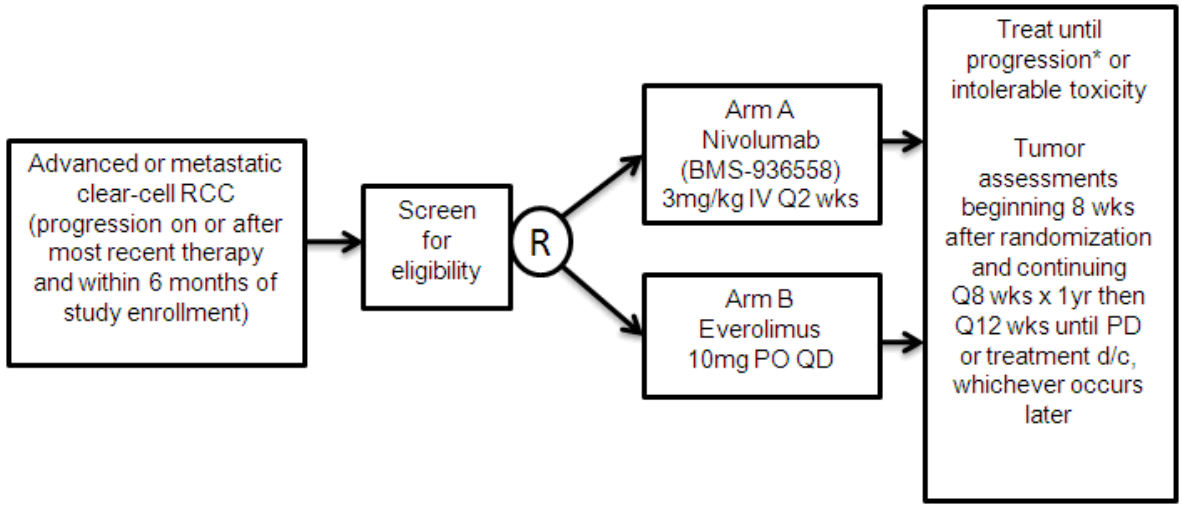
Key Inclusion criteria	Key exclusion criteria
Men and women aged ≥18 years who signed informed consent and met the following criteria were enrolled: • Histologically confirmed advanced or metastatic RCC with a clear-cell component; • Measurable disease according to RECIST v1.1; • Received one or two previous regimens of anti-angiogenic therapy; • No more than three total previous regimens of systemic therapy; • Disease progression during or after the last treatment regimen and within 6 months before study enrolment; • Karnofsky PS ≥70	Patients who met any of the following key criteria were excluded from study eligibility: • Metastasis to the CNS; • Previous treatment with an mTOR inhibitor; • Condition requiring treatment with glucocorticoids (equivalent to >10mg prednisone daily)
Abbreviations in table: CNS, central nervous system; MTOR, Mammalian target of rapamycin; PS, performance status; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours	

After screening, patients recruited into CheckMate 025[37, 39] were randomised in a 1:1 ratio to receive nivolumab 3 mg/kg of body weight intravenously every 2 weeks or 10 mg everolimus orally once daily. Randomisation was stratified by Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk group, and the number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting. In addition, the CS (pg 57, Section 4.3, Table 9) states that, "Patients were treated until progression or unacceptable toxicity. Patients were allowed to continue the study therapy after initial disease progression if a clinical benefit as assessed by the investigator was noted and the study

drug had an acceptable side-effect profile. Dose modifications were not permitted for nivolumab, but were permitted for everolimus". Patients who continued treatment after progression discontinued therapy when further progression was documented (CSR, pg 55, Section 3.1).

Dose delays were permitted for nivolumab and everolimus for up to 6 weeks from the last dose. Delays longer than 6 weeks were allowed only in order to manage drug-related AEs, or in some cases if the delay was due to a non-drug related cause. Figure 3 shows the study design of CheckMate 025.

Figure 3. CheckMate 025 study design (reproduced from CSR, pg 3, Figure 1)



Abbreviation in figure: BMS, Bristol-Myers Squibb; CSR, clinical study report; D/C, discontinuation; IV, intravenous/intravenously; PD, progressive disease; PO, per os (by mouth); Q2wks, every 2 weeks; R, randomisation; RCC, renal cell carcinoma.
Source: CheckMate 025 CSR [39]

The primary outcome of CheckMate 025[37, 39] was:

- Overall survival (OS), defined as the time from randomisation to the date of death.

Secondary outcomes were:

- Progression-free survival (PFS), defined as the time from randomisation to first documented RECIST-defined tumour progression or death from any cause;
- Objective response rate (ORR), defined as the number of patients with a complete response or a partial response divided by the number of patients who underwent randomisation;
- Adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0;
- Health related quality of life (HRQoL) assessed using FKSI-DRS questionnaire and EQ-5D.

With the exception of safety results, all outcomes in CheckMate 025 are reported for the ITT population and based on the company's clinical database lock of 18th June 2015. OS assessments were performed continuously during treatment and every three months during follow-up. Disease

assessments (PFS, ORR) were performed every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment. Safety assessments were conducted at each clinic visit, and HRQoL was assessed after randomisation and prior to dosing Day 1 of each cycle beginning with cycle 2. Table 7 summarises the methodology of CheckMate 025.

The ERG considers CheckMate 025 to be well conducted but notes that there were high rate of discontinuation in the two groups: nivolumab (339/410) and everolimus (369/411).

Table 7. Summary of trial methodology of CheckMate 025 (reproduced from CS, pg 56, Table 9)

	CheckMate 025
Location	Patients were treated at 146 sites in 24 countries including Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Norway, Poland, Romania, Russian Federation, Spain, Sweden, United Kingdom and United States
Trial design	A Phase III, randomised, open-label, active control, multi-centre clinical trial Patients were randomised 1:1 through an IVRS. Randomisation was stratified by MSKCC risk group, and number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting
Eligibility criteria for participants	Men and women aged ≥18 years who signed informed consent and met the following criteria were enrolled: • Histologically confirmed advanced or metastatic RCC with a clear-cell component; • Measurable disease according to RECIST v1.1; • Received one or two previous regimens of anti-angiogenic therapy; • No more than three total previous regimens of systemic therapy; • Disease progression during or after the last treatment regimen and within 6 months before study enrolment; • Karnofsky PS ≥70 Patients who met any of the following key criteria were excluded from study eligibility: • Metastasis to the CNS; • Previous treatment with an mTOR inhibitor; • Condition requiring treatment with glucocorticoids (equivalent to >10mg prednisone daily)
Settings and locations where the data were collected	Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. The DMC acted in an advisory capacity to BMS, monitoring subject safety and evaluating the available efficacy data for the study.
Trial drugs	Nivolumab group (n=410): nivolumab 3mg/kg by IV infusion every 2 weeks Everolimus group (n=411): everolimus administered orally at a daily dose of 10mg Patients were treated until progression or unacceptable toxicity. Patients were allowed to continue the study therapy after initial disease progression if a clinical benefit as assessed by the investigator was noted and the study drug had an acceptable side-effect profile. Dose modifications were not permitted for nivolumab, but were permitted for everolimus.
Permitted and disallowed concomitant	Immunosuppressive agents, systemic corticosteroids and any concurrent antineoplastic therapy were prohibited during the study. Live vaccines were to be avoided wherever possible.

	CheckMate 025
medication	Patients were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids. Physiologic replacement doses of systemic corticosteroids were permitted, even if >10mg/day prednisone equivalent. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions was permitted. Patients were allowed to continue hormone replacement therapy if initiated prior to randomisation. Bisphosphonates and RANK L inhibitors were allowed for bone metastases if initiated prior to randomisation. Supportive care for disease-related symptoms could be offered to all patients on the trial. Palliative (limited-field) radiation therapy and palliative surgical resection was permitted if certain criteria were met.
Primary outcomes	OS: defined as the time from randomisation to the date of death Assessments for survival were performed continuously during treatment and every 3 months during follow-up.
Secondary	ORR: defined as the number of patients with a complete response or a partial response divided by the number of patients who underwent randomisation; PFS: defined as the time from randomisation to first document RECIST-defined tumour progression or death from any cause; Association between OS and tumour expression of PD-L1 (≥1% vs <1% and ≥5% vs <5%); Adverse events: graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; HRQL: assessed using the FKSI-DRS questionnaire Disease assessments were performed every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment. Safety assessments were conducted at each clinic visit. HRQL assessments were performed after randomisation and prior to dosing on Day 1 of each cycle beginning with Cycle 2.
Exploratory outcomes	Pharmacokinetic characterisation of nivolumab including exploration of the exposure-response relationship; Immunogenicity characterisation of nivolumab; Biomarker assessment to identify potential predictive biomarkers of efficacy other than PD-L1 expression status; Genetic characterisation to assess the effect of natural variation SNPs in select genes on clinical and safety endpoints; HRQL: assessed using the EQ-5D tool; Health resource utilisation: assessed during the study and at the first two follow-up visits
Pre-planned subgroups	Subgroup analyses assessing the effects of baseline MSKCC risk group (and Heng risk group), number of prior anti-angiogenic therapies, age category, type and duration of prior therapy, number and site of metastases were all pre-planned.

Abbreviations in table: CNS, central nervous system; EQ-5D, EuroQoL 5-Dimension; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; HRQL, health-related quality of life; IV, intravenous; IVRS, interactive voice response system; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, overall response rate; OS, overall survival; PD-L1, programmed death receptor ligand 1; PFS, progression-free survival; PS, performance status; RCC, renal cell carcinoma; SNPs, single nucleotide polymorphisms.

CheckMate 010[65] is a phase II, randomised, double-blinded, multicentre dose-ranging trial of nivolumab in patients with clear-cell advanced RCC after prior anti-angiogenic therapy. A total of 168 patients from 39 centres in North America and Europe were randomised to receive nivolumab 0.3 or 2 or 10 mg/kg by intravenous infusion every three weeks. The trial was conducted between May 2011 and January 2012.

CheckMate 003[66] is a phase 1b, open-label, dose-escalation trial of nivolumab in patients with selected advanced or recurrent malignancies, including RCC, who had received up to five prior systemic therapies. Between November 2008 and January 2012, 34 patients with pre-treated advanced RCC received nivolumab 1 mg/kg (n=18) or 10 mg/kg (n=16).

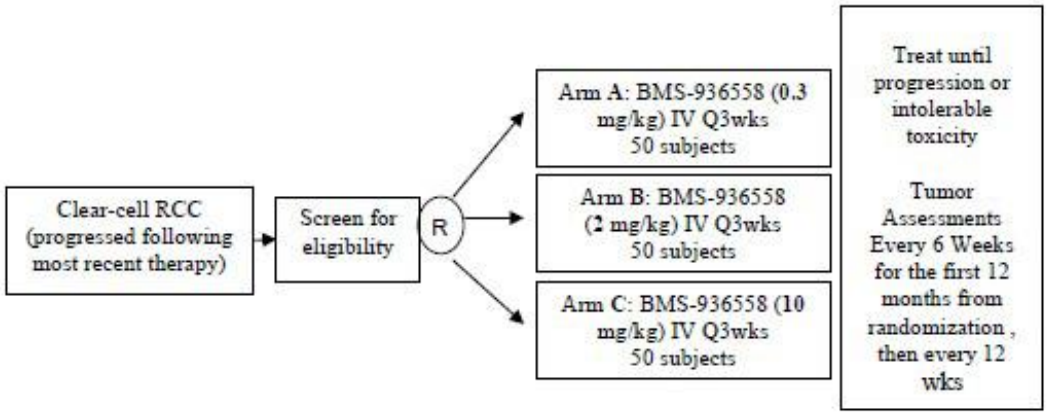
The main eligibility criteria of CheckMate 010[65] and CheckMate 003[66] are presented in Table 8.

Table 8. Eligibility criteria of CheckMate 010 and CheckMate 003 (adapted from CS, pg 106, Table 19)

Trial	Inclusion criteria	Exclusion criteria
CheckMate 010[65]	Adult patients with advanced RCC with a clear-cell component who had received prior treatment with at least one anti-angiogenic therapy	Patients with active CNS metastases, autoimmune disease, previous therapy with a T-cell co-stimulation or checkpoint inhibitor, or treatment with more than three prior treatment regimens in the metastatic setting.[65]
CheckMate 003[66]	Adult patients with treatment-refractory solid tumours including advanced RCC patients	Patients with a history of autoimmune disease, prior therapy with T-cell modulating antibodies (e.g. anti–PD-1, anti–PD-L1, anticytotoxic T-lymphocyte–associated antigen 4), conditions requiring immunosuppression, or chronic infections were excluded.[66]
Abbreviations in table: CNS, central nervous system; PD-1, programmed death ligand-1; RCC, renal cell carcinoma.		

In CheckMate 010[65] patients were treated until disease progression or unacceptable toxicity. Tumour assessments were performed every 6 weeks for 12 months and every 12 weeks thereafter while survival assessments were performed continuously during treatment and every 3 months during follow-up. Figure 4 shows the study design of CheckMate 010.

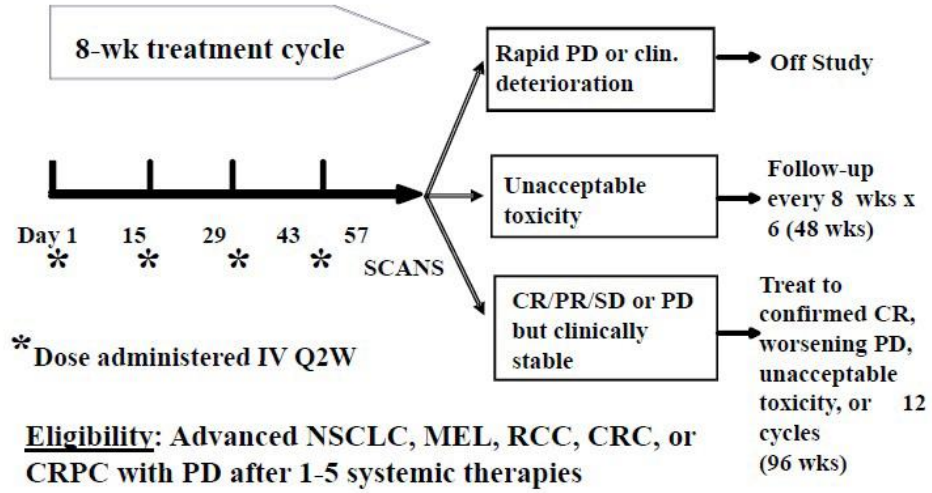
Figure 4. CheckMate 010 study design (reproduced from CheckMate 010 CSR, pg 33, Figure 3.1-1)



Abbreviations in figure: BMS, Bristol-Myers Squibb; CSR, clinical study report; IV, intravenous/intravenously; Q3wks, once every 3 weeks; R, randomisation; RCC, renal cell carcinoma.
Source: CheckMate 010 CSR[70]

In CheckMate 003,[66] during the dose-escalation phase patients received nivolumab 1, 3 or 10 mg/kg, but the advanced RCC population was treated with nivolumab 10 mg/kg in an initial expansion cohort, followed by a subsequent expansion cohort of 1 mg/kg. Treatment continued up to 96 weeks (12 cycles) or until patients experienced confirmed complete response, disease progression or unacceptable toxicity. Tumour assessments were performed after each 8-week treatment cycle and survival assessments were performed continuously during treatment and every 3 months during follow-up. Figure 5 shows the study design of CheckMate 003.

Figure 5. CheckMate 003 study design (reproduced from CheckMate 003 CSR, pg 2, Figure 3-1)



Abbreviations used in figure: CR, complete response; CRC, colorectal cancer; CRPC, castrate-resistant prostate cancer; IV, intravenous infusion; MEL, melanoma; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; RCC, renal cell carcinoma; SD, stable disease.
Source: CheckMate 003 CSR[71]

The ERG considers both CheckMate 010[65] and CheckMate 003[66] to be well conducted trials but highlights the high discontinuation rate in CheckMate 010[65] (nivolumab 0.3 mg/kg [50/60], nivolumab 2 mg/kg [49/54] and nivolumab 10 mg/kg [44/54]).

4.2.2 Baseline characteristics

The baseline characteristics (demographics and clinical) of participants in CheckMate 025[37, 39] were well balanced between the two treatment groups as presented in Table 9. In the CS (pg 129, Section 4.13), the company states that, "In the pivotal Phase III trial, European sites represented approximately half of all involved (69/146). This included four UK sites across which 26 patients were randomised." The ERG's clinical expert would not anticipate issues with applying CheckMate 025[37, 39] results to patients presenting in UK clinical practice as participants in the trial adequately reflect English clinical practice post first-line therapy for advanced RCC. The participant flow diagram of CheckMate 025 is shown in Appendix 10.2.

Table 9. Baseline characteristics of patients in CheckMate 025 (reproduced from CS, pg 65–66, Table 11, Section 4.5)

Baseline characteristic	Nivolumab (n=410)	Everolimus (n=411)
Age, median years (range)	62 (23-88)	62 (18-86)
Gender, male n (%)	315 (77)	304 (74)
Race, Caucasian n (%)	White: 353 (86) Asian: 42 (10) Black: 1 (<1) Other: 14 (3)	White: 367 (89) Asian: 32 (8) Black: 4 (1) Other: 8 (2)
MSKCC risk group, n (%)	Favourable: 145 (35) Intermediate: 201 (49) Poor: 64 (16)	Favourable: 148 (36) Intermediate: 203 (49) Poor: 60 (15)
IMDC risk group, n (%)	Favourable: 55 (13.4) Intermediate: 242 (59.0) Poor: 96 (23.4)	Favourable: 70 (17.0) Intermediate: 241 (58.6) Poor: 83 (20.2)
Karnofsky PS, n (%)	<70: 2 (<1) 70: 22 (5) 80: 110 (27) 90: 150 (37) 100: 126 (31)	<70: 1 (<1) 70: 30 (7) 80: 116 (28) 90: 130 (32) 100: 134 (33)
Common metastasis site, n (%)	Lung: 278 (68) Liver: 100 (24) Bone: 76 (19)	Lung: 273 (66) Liver: 87 (21) Bone: 70 (17)
Previous nephrectomy, n (%)	364 (89)	359 (87)
Time from initial diagnosis to randomisation, median months (range)	31 (1-392)	31 (2-372)
Previous anti-angiogenic regimens, n (%)	1: 294 (72) 2: 116 (28)	1: 297 (72) 2: 114 (28)
Previous anti-angiogenic therapy, n (%)	Sunitinib: 246 (60) Pazopanib: 119 (29) Axitinib: 51 (12)	Sunitinib: 242 (59) Pazopanib: 131 (32) Axitinib: 50 (12)
Patients with quantifiable PD-L1 expression, n (%):	Yes: 370 (90) No: 40 (10)	Yes: 386 (94) No: 25 (6)
PD-L1 expression level, n (%):	≥1%: 94 (25) <1%: 276 (75) ≥5%: 44 (12) <5%: 326 (88)	≥1%: 87 (23) <1%: 299 (77) ≥5%: 41 (11) <5%: 345 (89)
Abbreviations in table: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Centre; PD-L1, programmed death receptor ligand 1; PS, performance status; SD, standard deviation.		

In CheckMate 010,[65] baseline characteristics were balanced among the treatment groups. More than 70% of patients in CheckMate 010 had received more than one prior systemic therapy for metastatic RCC and 25% of patients had poor MSKCC risk score. Table 10 summarises the baseline characteristics of CheckMate 010.

Table 10. Baseline characteristics of patients in CheckMate 010 (reproduced from CS, pg 109, Table 21, Section 4.11)

Baseline characteristic	Nivolumab 0.3 mg/kg (n=60)	Nivolumab 2 mg/kg (n=54)	Nivolumab 10 mg/kg (n=54)
Age, median years (range)	61 (9)	61 (8)	61 (10)
Gender, male n (%)	41 (68)	40 (74)	40 (74)
MSKCC risk group, n (%) Favourable Intermediate Poor	 20 (33) 26 (43) : 14 (23)	 18 (33) 22 (41) : 14 (26)	 18 (33) 22 (41) 14 (26)
Karnofsky PS, n (%) 70 or 80 90 or 100	 22 (37) 38 (63)	 30 (56) 24 (44)	 25 (46) 28 (52)
Common metastasis site, n (%)	Lung: 46 (77) Lymph node: 29 (48) Liver: 15 (25) Skin/soft tissue: 18 (30) Adrenal: 8 (13)	Lung: 39 (72) Lymph node: 35 (65) Liver: 13 (24) Skin/soft tissue: 11 (20) Adrenal: 19 (35)	Lung: 39 (72) Lymph node: 34 (63) Liver: 19 (35) Skin/soft tissue: 11 (20) Adrenal: 10 (19)
Previous anti-angiogenic regimens, n (%)	1: 34 (57) 2: 22 (37) 3: 4 (7)	1: 35 (65) 2: 16 (30) 3: 3 (6)	1: 35 (65) 2: 18 (33) 3: 1 (2)
Previous systemic therapy, n (%)	Sunitinib: 46 (7) Everolimus: 21 (35) Pazopanib: 15 (25) IL-2: 15 (25) Sorafenib: 13 (22)	Sunitinib: 42 (78) Everolimus: 18 (33) Pazopanib: 18 (33) IL-2: 11 (20) Sorafenib: 8 (15)	Sunitinib: 37 (69) Everolimus: 18 (33) Pazopanib: 13 (24) IL-2: 12 (22) Sorafenib: 19 (31)
Abbreviations used in table: MSKCC, Memorial Sloan-Kettering Cancer Centre; PD-L1, programmed death receptor ligand 1; PS, performance status; SD, standard deviation.			

In CheckMate 003,[66] 71% of patients had received at least two prior systemic treatments for RCC, 71% had received anti-angiogenic therapy, 71% had received immunologic, biologic, or hormone therapy; and 32% had received mTOR inhibitor. Table 11 summarises the baseline characteristics of CheckMate 003.

Table 11. Baseline characteristics of patients in CheckMate 003 (reproduced from CS, pg 112, Table 22, Section 4.11)

Baseline characteristic	Nivolumab (n=34)
Age, median years (range)	58 (35-74)
Gender, male n (%)	26 (76)
ECOG PS, n (%)	0: 17 (50) 1: 17 (50)
Common metastasis site, n (%)	Bone: 10 (29) Liver: 9 (27) Lung: 30 (88) Lymph node: 28 (82) Any visceral site: 30 (88)
Prior anti-angiogenic treatment, n (%)	24 (71)

Baseline characteristic	Nivolumab (n=34)
Previous systemic regimens, n (%)	1: 10 (29) 2: 9 (27) 3: 6 (18) ≥4: 9 (27)
Previous systemic therapy, n (%)	Hormonal, immunologic, or biologic: 24 (71) Chemotherapy: 19 (56) mTOR inhibitor: 11 (32) Radiotherapy: 10 (29)
Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; PS, performance status; RCC, renal cell carcinoma.	

4.2.3 Description and critique of statistical approach used

In CheckMate 025,[37, 39] it was initially planned that an interim analyses would be conducted after 398/569 deaths (70%), and a final analysis was planned after 569 deaths. This was based on 90% power to detect a hazard ratio (HR) of 0.76 with type I error of 0.05. However, the study was stopped in July 2015 after an assessment by the independent data monitoring committee decided that a significant improvement in OS had been achieved.

The intention-to-treat (ITT) population in CheckMate 025 used for the primary efficacy analysis included all patients who were randomised to either group, and safety analyses included all patients who received at least one dose of study medication. In addition, standard censoring methods were used to account for missing data in primary OS and PFS analysis.

Pre-specified subgroup analyses in CheckMate 025[37, 39] were conducted to assess the effects of baseline characteristics including MSKCC risk group (and Heng risk group), number of prior anti-angiogenic therapies, type and duration of prior therapy, and number and site of metastases on treatment. Table 12 details the statistical analysis including sample size and power calculations for CheckMate 025.[37, 39]

Table 12. Summary of statistical analysis in CheckMate 025 (reproduced from CS, pg 60, Section 4.4, Table 10).

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with nivolumab monotherapy will improve overall survival compared to everolimus monotherapy in patients with advanced RCC	OS, PFS and DOR estimated with the use of KM methods. Medians and corresponding 95% CIs were determined with Brookmeyer and Crowley methods; 95% CIs were constructed by means of a log–log transformation.	The sample size was calculated in order to compare the OS between subjects randomised to receive nivolumab and subjects randomised to receive everolimus. The final analysis was planned to take place after 569 events (i.e. deaths). Approximately 569 deaths provides 90% power to detect a HR of 0.76 with an overall type 1 error of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab.	For patients who had not died, OS was censored at last known date alive. For patients who did not progress or die, PFS and DOR was censored on the date of the last evaluable tumour assessment. Patients who did not have any on-study

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	A stratified log-rank test was performed to compare the nivolumab group with the everolimus group with respect to OS and PFS. A stratified HR and CI for nivolumab vs everolimus was obtained by fitting a stratified Cox model with the group variable as a single covariate. The difference in ORR between the nivolumab group and the everolimus group along with the two-sided 95% CI were estimated with the CMH method of weighting, with adjustment for the stratification factors	Approximately 822 subjects were therefore to be randomised to the two arms in a 1:1 ratio. Pre-planned interim analysis was conducted after 398 of the 569 deaths (70%) required for the final analysis had occurred; the stopping boundary was derived on the basis of the number of deaths with the use of an O'Brien–Fleming alpha-spending function that provided 90% power to detect a hazard ratio of 0.76 with an overall type I error rate of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. The stopping boundaries at interim and final analyses were to be derived based on the number of deaths using O'Brien and Fleming alpha-spending function. It was projected that an observed HR of 0.845 or less, which corresponds to a 2.7 months or greater improvement in median OS (14.8 vs 17.5 months), would result in a statistically significant improvement in OS for nivolumab at the final OS analysis.	tumour assessments and did not die were to be censored on the date they were randomised.
Abbreviations in table: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; DOR, duration of response; HR, hazard ratio; KM, Kaplan Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial			

In CheckMate 010,[65] sample size calculation was based on 150 patients to provide ≥90% power to detect a dose-response relationship across the treatment arms (assuming median PFS was 4.0, 5.7, and 8.1 months for nivolumab 0.3, 2, and 10 mg/kg respectively). It was expected that with about 150 patients, accrual would be completed after 10 months, and final analysis of PFS could be conducted 19 months after start of study. Evaluation of dose relationship was performed using a two-sided 20%-level Cochran-Armitage test. The stratified (MSKCC risk group, the number of prior anti-angiogenic therapies, and the region) OS comparison between the treatment groups was estimated using Cox proportional hazards model which utilises the randomised group as a single covariate. Median OS and 80% confidence interval (CI) for each treatment group was estimated using Kaplan Meier (KM) methodology. ORR was estimated along an 80% CI using the Clopper-Pearson method.

In CheckMate 003,[66] objective tumour response and stable disease rates were estimated using the Clopper-Pearson method. PFS, OS, survival rates and response duration were estimated using KM method with CIs for OS and PFS rates based on the Greenwood formula.

Overall, the ERG considers the statistical approaches used for the analyses of outcome data in CheckMate 025, CheckMate 010, and CheckMate 003 to be appropriate and robust.

4.2.4 Summary statement

The company identified one RCT (CheckMate 025[37, 39]) from the systematic review that provided direct evidence addressing part of the decision problem as outlined in the NICE final scope.[23] CheckMate 025[37, 39] compared nivolumab with everolimus in patients with clear cell advanced RCC who had received previous anti-angiogenic therapy. The outcomes assessed in CheckMate 025 (OS, PFS, ORR, adverse events, HRQoL) and presented in the CS are clinically relevant and address the decision problem as outlined in the NICE final scope.[23]

In addition to, the company identified one randomised dose-ranging trial (CheckMate 010[65]) and one randomised dose-escalation trial (CheckMate 003[66]) from its internal clinical trial database to supplement the RCT data in the use of nivolumab in advanced RCC.

The primary objective of CheckMate 010[65] was to evaluate the dose-response relationship of nivolumab as measured by PFS; secondary outcomes included ORR, OS and safety. CheckMate 003[66] reported the OS, and long term safety profile in patients advanced RCC in patients receiving nivolumab, with a minimum of 78 weeks since treatment initiation.

In summary, the ERG considers the evidence provided by the company to inform one part of the decision problem: nivolumab compared with everolimus, to be of relatively high quality. Although, the key trial, CheckMate 025 was an open label study. Overall, the ERG considers the choice of outcomes and statistical approach used for the analyses of outcome data in CheckMate 025, 010 and 003 to be adequate.

4.3 Clinical effectiveness results

The company presented the clinical effectiveness results for CheckMate 025[37, 39] (CS, Section 4.7), CheckMate 010[65] and CheckMate 003[66] (CS, Section 4.11).

The primary outcome in CheckMate 025[37, 39] was OS, and secondary outcomes included PFS, ORR, AEs and HRQoL. The ITT analysis (included all patients who were randomised to either treatment group) was used for the primary efficacy (OS) analysis, and safety analysis was based on all-treated population which included all patients who received at least one dose of study medication. All analyses were based on the company's clinical database lock of 18 June 2015.

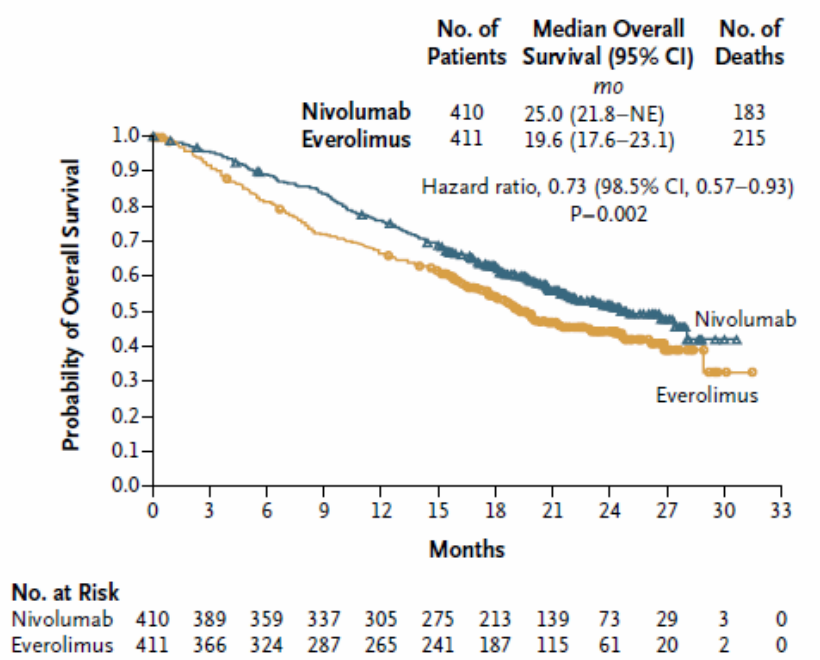
The primary outcome in CheckMate 010[65] was PFS, and secondary outcomes included ORR, OS and safety. The efficacy population in CheckMate 010 included all randomly assigned patients. Data presented for CheckMate 010 are from the primary data cut-off of 15 May 2013 for PFS and ORR analyses and from an updated data cut-off of 5 April 2015 for OS analysis, providing a minimum follow-up of 38 months for all patients.

The primary objective in CheckMate 003[66] was to assess the safety and tolerability of nivolumab, but OS was included as an exploratory endpoint based on observed objective response. Other outcomes included stable disease, PFS, and response duration. The efficacy population included all randomly assigned patients.

4.3.1 OS

With a median follow-up of 17.2 to 18.3 months across treatment groups, median OS in CheckMate 025[37, 39] was longer in nivolumab treated patients (25.0 months, 95% CI: 21.8 to not estimable) compared with everolimus treated patients (19.6 months, 95% CI: 17.6 to 23.1) (Figure 6).

Figure 6. Kaplan Meier curve for OS in Checkmate 025 (reproduced from CS, pg 68, Figure 8, Section 4.7)



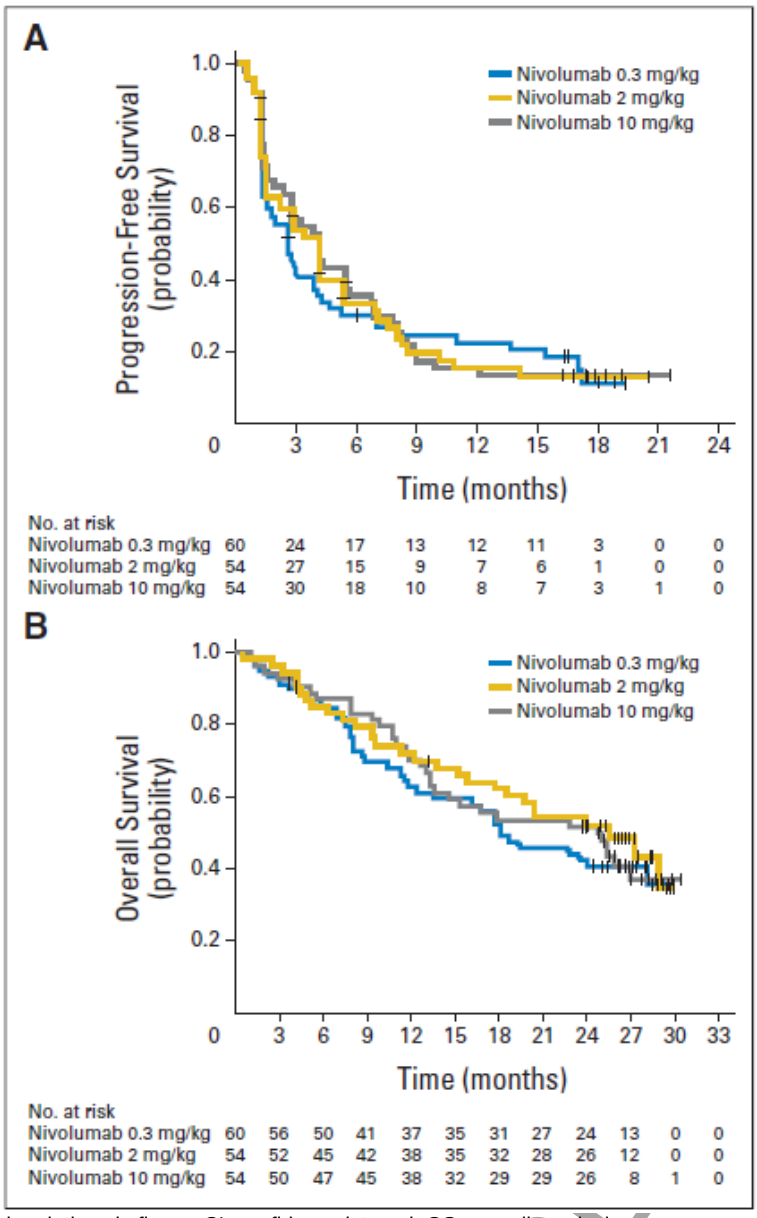
Abbreviations in figure: CI, confidence interval; mo, months; NE, not estimable.

The hazard ratio (HR) for death from any cause showed better OS benefit of nivolumab compared with everolimus (HR 0.73, 95% CI: 0.57 to 0.93; p=0.002).[37, 39] In addition, there were 184/410 (45%) deaths in the nivolumab group compared with 215/411 (52%) in the everolimus group.[37, 39] Survival rate at 6 months was 89% (95% CI: 85.7% to 91.8%) in the nivolumab group and 81% (95 CI: 77.0% to 84.7%) in the everolimus group, and at 1-year it was 76% (95% CI: 71.5% to 79.9%) in the nivolumab group and 67% (95% CI: 61.8% to 71.0%) in the everolimus group.[37, 39] According to the CS (pg 95-6, Section 4.10.3), proportional hazards were observed in OS between nivolumab and everolimus in CheckMate 025. However, the ERG does not agree with this statement as the survival curves for the two treatments cross and only separate after around 1.5 months (Figure 6). This issue is more explicitly tested by the ERG in Section 5.5.5.1.

It is also reported in the CS (pg 96, Section 4.10.3) that nivolumab did not show a curative effect in CheckMate 025, and the reasons provided by the company included insufficient follow-up and/or sample size not powered enough to detect such an effect. However, the ERG's clinical experts are of the view that it may also be due to the mechanism of action of nivolumab. It takes time for the host response to be engaged with immunotherapies such as nivolumab whereas targeted agents such as everolimus exert their effect more rapidly. Potentially immunotherapies may achieve a plateau at a higher survival rate than targeted agents or chemotherapy, as demonstrated by the use of ipilimumab in melanoma.[72]

In CheckMate 010,[65] median OS was 18.5 months (80% CI: 16.2 to 24.0 months) in the nivolumab 0.3 mg/kg group, 25.5 months (80% CI: 19.8 to 31.2 months) in the nivolumab 2 mg/kg group, and 24.8 months (80% CI: 15.3 to 26.0 months) in the nivolumab 10 mg/kg group (Figure 7). Three year OS rates were 33-44% depending on the nivolumab dose.[73]

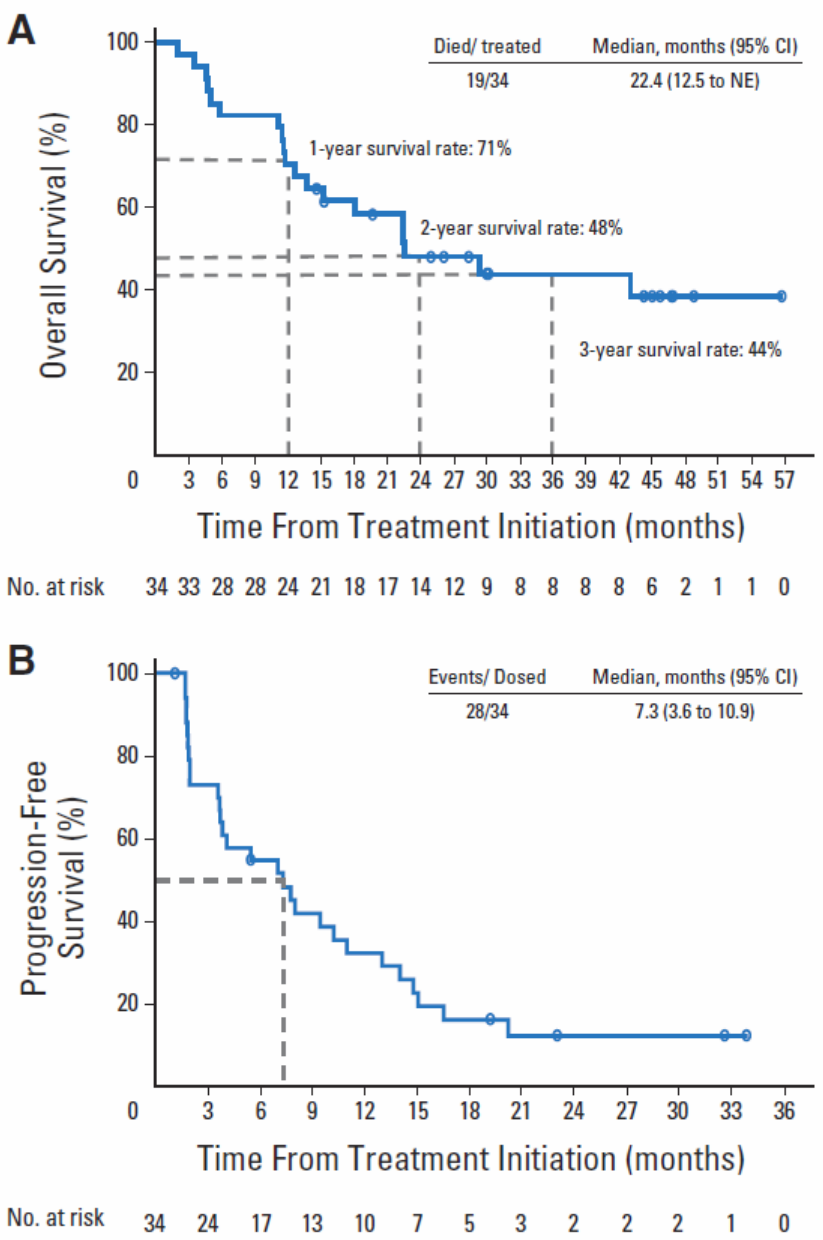
Figure 7. Kaplan Meier curves for OS and PFS in Checkmate 010, all randomised patients



Abbreviations in figure: CI, confidence interval; OS, overall survival
Source: Motzer *et al.* 2014[65]

Median OS in advanced RCC patients in CheckMate 003[66] was 22.4 months in patients receiving nivolumab 1 or 10 mg/kg, and survival rate was 71% at 1 year, 48% at 2 years, and 44% at 3 years (Figure 8).

Figure 8. Kaplan Meier curves for OS and PFS in Checkmate 003, advanced RCC patients (reproduced from CS, pg 114, Figure 21A, Section 4.11)

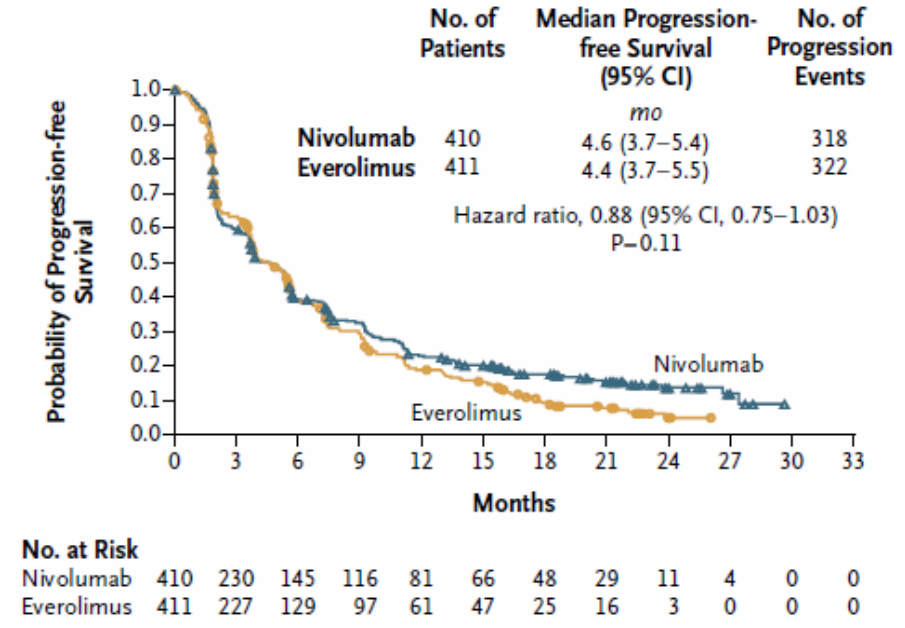


Abbreviations in figure: CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival

4.3.2 PFS

The median PFS in CheckMate 025[37, 39] was not statistically significant between nivolumab (4.6 months, 95% CI: 3.7 to 5.4) and everolimus (4.4 months, 95% CI: 3.7 to 5.5) groups, and the HR for death or progression in nivolumab compared with everolimus (HR 0.88, 95% CI: 0.75 to 1.03, p=0.11).[37, 39] The 6-month PFS was 39% in both the nivolumab and everolimus groups, and at 1 year it was 23% in the nivolumab and 19% in the everolimus groups.[37, 39] Figure 9 shows the KM curve for PFS in CheckMate 025.

Figure 9. Kaplan Meier curve for PFS in Checkmate 025 (reproduced from CS, pg 69, Figure 9, Section 4.7)



Abbreviation used in figure: CI, confidence interval; mo, months.

According to the company (CS, pg 70, Section 4.7) the non-significant PFS results between the nivolumab and everolimus groups in CheckMate 025[37, 39] may be due to PFS being assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, which, according to the company is a conservative estimate of PFS because it does not take into account "tumour flare". Tumour flare is a result of the immune response to immunotherapies like nivolumab and may be misinterpreted as progression. This phenomenon has been termed "pseudo-progression". However, while the ERG's clinical experts consider that in theory the RECIST criteria may be conservative, they also consider pseudo-progression to be rare in clinical practice. The ERG notes that proportional hazards were not observed for PFS in CheckMate 025, therefore summarising the treatment effect with a HR may be misleading. The ERG explores the absence of proportional hazards for PFS more thoroughly in Section 5.5.5.2.

In CheckMate 010, median PFS was 2.7 months (80% CI: 1.9 to 3.0 months) in the nivolumab 0.3 mg/kg group, 4.0 months (80% CI: 2.8 to 4.2 months) in the nivolumab 2 mg/kg group, and 4.2 months (80% CI: 2.8 to 5.5 months) in the nivolumab 10 mg/kg group.[65, 73] Figure 7(B) shows the KM curve for PFS in CheckMate 010 for all randomised patients.

Median PFS for advanced RCC patients in CheckMate 003[66] was 7.3 months, with 1-year PFS rate of 35% and 2-year PFS rate of 12%. Figure 8(B) shows the KM curve for PFS in CheckMate 003 for advanced RCC patients.

4.3.3 Objective response rate (ORR)

In the ITT population of CheckMate 025,[37, 39] investigator-assessed ORR using the RECIST criteria was significantly higher (25%) in the nivolumab compared with everolimus group (5%) (odds ratio [OR] 5.98; 95% CI: 3.68 to 9.72; p<0.001).[37, 39] Four patients in the nivolumab group achieved complete response compared with two patients in the everolimus group. The ORR with a confirmatory scan after ≥4 weeks (that is, confirmed ORR) was also significantly superior (p<0.001) in the nivolumab group (22%) compared with the everolimus group (4%). Table 13 summarises the response analyses in CheckMate 025.

Table 13. Investigator assessed best overall response, ITT analysis in CheckMate 025 (reproduced from CS, pg 73, Section 4.7, Table 13)

	Nivolumab (n=410)	**Everolimus (n=411)**
ORR, n (%)	103 (25.1)	22 (5.4)
OR (95% CI)	5.98 (3.68-9.72)	
p-value	<0.0001	
Best overall response, n (%)		
CR	4 (1.0)	2 (0.5)
PR	99 (24.1)	20 (4.9)
Median time to response, months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
Median duration of response, months (range)	12.0 (0-27.6)	12.0 (0-22.2)
Abbreviations in table: CI, confidence interval; CR, complete response; OR, odds ratio; ORR, objective response rate; PR, partial response.		

The median time to response (3.5 months [range: 1.4 to 24.8] in the nivolumab group, and 3.7 months [range: 1.5 to 11.2] in the everolimus group) was similar across both treatment groups and the duration of the response was 12 months for both groups. In the CS (pg 56–58, Section 4.3, Table 9) the company states, "Patients were treated until progression or unacceptable toxicity. Patients were allowed to continue the study therapy after initial disease progression if a clinical benefit as assessed by the investigator was noted and the study drug had an acceptable side-effect profile". The ERG's clinical experts agreed that treatment beyond progression was likely to occur in clinical practice if a patient was responding to treatment without intolerable side effects.

In CheckMate 010,[65] there was consistent ORR regardless of the dose: 20% in nivolumab 0.3 mg/kg, 22% in nivolumab 2 mg/kg, and 20% in the nivolumab 10 mg/kg group. Median duration of response (DOR) in CheckMate 010 was reached only in the nivolumab 10 mg/kg group (22.3 months, CI: 4.8 to not reached), and 40% of patients were still responding to nivolumab treatment 2 years after treatment initiation.

In CheckMate 003[66], ORR was observed in 29% (10/34) of advanced RCC patients treated with either nivolumab 1 mg/kg or 10 mg/kg; an additional 27% (9/34) of patients experienced stable disease lasting 24 weeks, and 10 out of 34 patients achieved complete or partial response at median duration of 12.9 months (80% CI: 8.4 to 29.1 months).

4.3.4 HRQoL

In Checkmate 025,[37, 39] HRQoL was assessed using the FKSI-DRS and EQ-5D instruments. The median FKSI-DRS score at baseline was 31.0 during the first year in both treatment groups. Thereafter there was significant improvement in HRQoL in the nivolumab group compared with the everolimus group. In addition, a higher proportion of patients in the nivolumab group (55%) experienced meaningful improvement in FKSI-DRS (defined as ≥2-point increase) compared with 37% of patients in the everolimus group (p<0.001).

Table 14. FKSI-DRS completion rate and median change from baseline in CheckMate 025 (reproduced from CS, pg 78, Section 4.7, Table 14)

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	Completion rate, %	Median CFB (range)	Completion rate, %	Median CFB (range)	
Baseline	89	-	86	-	-
Week 4	87	0 (-13.0-11.0)	85	-1.0 (-20.0019.0)	<0.001
Week 8	87	0.0 (-13.0–14.0)	85	-1.0 (-19.0016.0)	<0.001
Week 12	85	0.0 (-19.0-17.0)	89	-1.0 (-18.0-19.0)	<0.001
Week 16	86	0.0 (-16.0-13.0)	89	-1.0 (-17.0-16.0)	<0.001
Week 20	86	0.0 (-11.0-16.0)	89	-1.0 (-16.0-16.0)	<0.001
Week 24	86	0.0 (-10.0-15.0)	87	-1.0 (-13.0-16.)	<0.001
Week 28	86	0.0 (-9.0-12.0)	88	-1.0 (-13.0-14.0)	<0.001
Week 32	88	1.0 (-9.0-15.0)	81	-1.0 (-11.0-15.0)	<0.001
Week 36	84	1.0 (-15.0-18.0)	85	-1.0 (-11.0-15.0	<0.001
Week 40	83	1.0 (-11.0-11.0)	84	-1.0 (-12.0-20.0)	<0.001
Week 44	83	1.0 (-11.0-16.0)	79	-1.0 (-10.0-18.0)	<0.001
Week 48	84	1.0 (-9.0-17.0)	81	-1.0 (-12.0-25.0)	<0.001
Week 52	80	1.0 (-9.0-17.0)	81	0.0 (-10.0-20.0)	<0.001
Week 56	81	1.0 (-7.0-17.0)	80	-1.0 (-17.0-17.0)	<0.001
Week 60	84	1.0 (-10.0-17.0)	79	-1.0 (-10.0-20.0)	<0.001
Week 64	78	1.0 (-9.0-16.0)	76	-1.0 (-8.0-12.0)	<0.001
Week 68	77	2.0 (-7.0-18.0)	73	-1.0 (-10.0-22.0)	<0.001
Week 72	76	1.0 (-6.0-16.0)	71	0.0 (-10.0-9.0)	0.001
Week 76	77	1.0 (-9.0-16.0)	76	0.0 (-10.0-19.0)	0.011
Week 80	76	2.0 (-5.0-11.0)	73	-1.0 (-10.0-25.0)	0.003
Week 84	74	1.5 (-6.0-16.0)	75	0.0 (-15.0-24.0)	0.002
Week 88	80	2.0 (-6.0-16.0)	65	0.0 (-12.0-22.0)	0.005
Week 92	71	3.0 (-4.0-18.0)	60	-1.0 (-12.0-21.0)	0.012
Week 96	81	2.0 (-1.0-7.0)	63	-2.5 (-12.0-20.0)	0.003
Week 100	79	3.0 (-2.0-10.0)	64	-3.0 (-12.0-12.0)	0.002

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	Completion rate, %	Median CFB (range)	Completion rate, %	Median CFB (range)	
Week 104	77	2.0 (-1.0-16.0)	90	-2.0 (-7.0-15.0)	0.019
Abbreviations in table: CFB, change from baseline. Notes: [a]between-group comparison for median change from baseline					

In the CS (pg 79, Section 4.7), the company states that a significant difference in EQ-5D visual analogue scale (VAS) between treatment groups were observed from weeks 4 through 68, weeks 76 through 80, and weeks 88 through 92. However, the ERG notes from the CS (Appendix 6, pg 104, Table 15) that significant improvement in HRQOL in the VAS scale only occurred in the nivolumab group compared with everolimus group from weeks 8 to 68 as shown by the p-values in Table 15.

Table 15. Descriptive statistics for EQ-5D VAS in CheckMate 025 (reproduced from CS, pg 104, Appendix 6, Table 15)

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	N	Median CFB (range)	N	Median CFB (range)	
Baseline	360	76.0 (0, 100)	343	78.0 (19, 100)	-
Week 4	335	0.0 (-80, 90)	313	0.0 (-65, 55)	0.122
Week 8	302	0.0 (-55, 89)	271	-1.0 (-59, 51)	<0.001
Week 12	265	1.0 (-45, 80)	220	0.0 (-61, 39)	<0.001
Week 16	236	1.5 (-56, 89)	192	-0.5 (-56, 39)	<0.001
Week 20	208	1.0 (-61, 90)	157	-1.0 (-61, 46)	<0.001
Week 24	186	2.0 (-39, 88)	143	-2.0 (-61, 41)	<0.001
Week 28	164	1.0 (-36, 80)	122	-2.5 (-50, 70)	<0.001
Week 32	158	3.0 (-45, 92)	102	-1.0 (-70, 51)	<0.001
Week 36	144	4.0 (-45, 69)	97	-1.0 (-45, 50)	<0.001
Week 40	132	4.0 (-40, 79)	87	-2.0 (-45, 59)	<0.001
Week 44	120	2.0 (-49, 80)	74	-1.0 (-41, 47)	0.022
Week 48	112	0.5 (-30, 79)	73	-2.0 (-49, 49)	0.002
Week 52	98	4.5 (-36, 78)	63	-2.0 (-36, 29)	<0.001
Week 56	91	3.0 (-51, 80)	58	-2.5 (-42, 32)	<0.001
Week 60	90	2.0 (-50, 75)	49	-4.0 (-40, 30)	<0.001
Week 64	82	4.0 (-20, 80)	44	-1.5 (-40, 30)	0.002
Week 68	73	5.0 (-10, 75)	35	-5.0 (-42, 32)	<0.001
Week 72	64	1.5 (-31, 80)	30	0.0 (-37, 40)	0.108
Week 76	60	4.5 (-22, 80)	28	0.5 (-44, 30)	0.091
Week 80	54	5.0 (-15, 80)	24	-1.5 (-41, 28)	0.085
Week 84	45	3.0 (-27, 84)	21	3.0 (-46, 28)	0.385
Week 88	44	4.5 (-21, 73)	15	0.0 (-36, 28)	0.096
Week 92	31	5.0 (-20, 53)	12	2.0 (-47, 35)	0.122
Week 96	30	5.0 (-12, 49)	12	2.5 (-39, 35)	0.443
Week 100	26	5.5 (-8, 50)	9	-8.0 (-40, 44)	0.034
Week 104	20	6.0 (-5, 53)	9	1.0 (-33, 46)	0.059
Abbreviations in table: CFB, change from baseline; EQ-5D, EuroQol-5 dimension; VAS, visual analogue scale. Notes: [a]between-group comparison for median change from baseline					

The company also reports in the CS (pg 79, Section 4.7) that the EQ-5D utility index showed significant benefit with nivolumab from weeks 8 through 12, weeks 24 through 44, weeks 52 through 68 and week 80. The ERG notes that significant benefit with nivolumab only occurred from weeks 8 through 12, and from weeks 24 through 68 as shown by the p-values in Table 16.

Table 16. Descriptive statistics for EQ-5D utility index in CheckMate 025 (reproduced from CS, pg 103, Appendix 6, Table 14)

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	N	Median CFB (range)	N	Median CFB (range)	
Baseline	360	0.796 (-0.261, 1.000)	344	0.796 (-0.074, 1.000)	-
Week 4	335	0.000 (-0.870, 0.970)	314	0.000 (-0.805, 0.741)	0.078
Week 8	303	0.000 (-0.775, 1.074)	272	0.000 (-0.945, 0.812)	0.014
Week 12	267	0.000 (-1.594, 0.970)	220	0.000 (-0.738, 0.741)	0.028
Week 16	237	0.000 (-0.812, 0.888)	192	0.000 (-0.777, 0.636)	0.179
Week 20	209	0.000 (-0.945, 1.074)	158	0.000 (-0.939, 0.626)	0.082
Week 24	187	0.000 (-0.713, 1.074)	143	0.000 (-0.848, 0.626)	0.021
Week 28	164	0.000 (-0.636, 1.074)	122	0.000 (-0.881, 0.626)	0.002
Week 32	158	0.000 (-0.568, 1.074)	102	0.000 (-0.972, 0.626)	0.002
Week 36	145	0.000 (-0.741, 0.918)	97	0.000 (-0.777, 0.626)	0.039
Week 40	133	0.000 (-0.532, 1.074)	87	0.000 (-1.022, 0.626)	0.012
Week 44	120	0.000 (-0.655, 1.074)	74	0.000 (-0.741, 0.626)	0.034
Week 48	113	0.000 (-0.707, 0.870)	73	0.000 (-1.016, 0.626)	0.052
Week 52	98	0.000 (-0.434, 1.074)	63	0.000 (-0.334, 0.626)	0.009
Week 56	91	0.000 (-0.434, 1.074)	58	0.000 (-0.413, 0.499)	0.003
Week 60	90	0.000 (-0.557, 1.074)	49	0.000 (-0.334, 0.532)	0.003
Week 64	82	0.000 (-0.434, 0.918)	44	0.000 (-0.812, 0.499)	0.001
Week 68	73	0.000 (-0.194, 1.074)	35	0.000 (-0.812, 0.532)	0.002
Week 72	64	0.000 (-0.434, 1.074)	30	0.000 (-0.741, 0.532)	0.113
Week 76	60	0.000 (-0.275, 1.074)	28	0.000 (-0.334, 0.568)	0.066
Week 80	54	0.000 (-0.298, 1.074)	24	0.000 (-0.841, 0.568)	0.031
Week 84	45	0.000 (-0.275, 1.074)	21	0.000 (-0.334, 0.568)	0.059
Week 88	44	0.000 (-0.309, 1.074)	15	0.000 (-0.334, 0.568)	0.166
Week 92	31	0.000 (-0.332, 1.074)	12	0.000 (-0.334, 0.568)	0.144
Week 96	30	0.044 (-0.766, 0.694)	12	0.000 (-0.768, 0.568)	0.228
Week 100	26	0.017 (-0.088, 1.074)	9	-0.071 (-0.768, 0.359)	0.019
Week 104	20	0.000 (-0.150, 1.074)	9	0.000 (-0.240, 0.359)	0.169

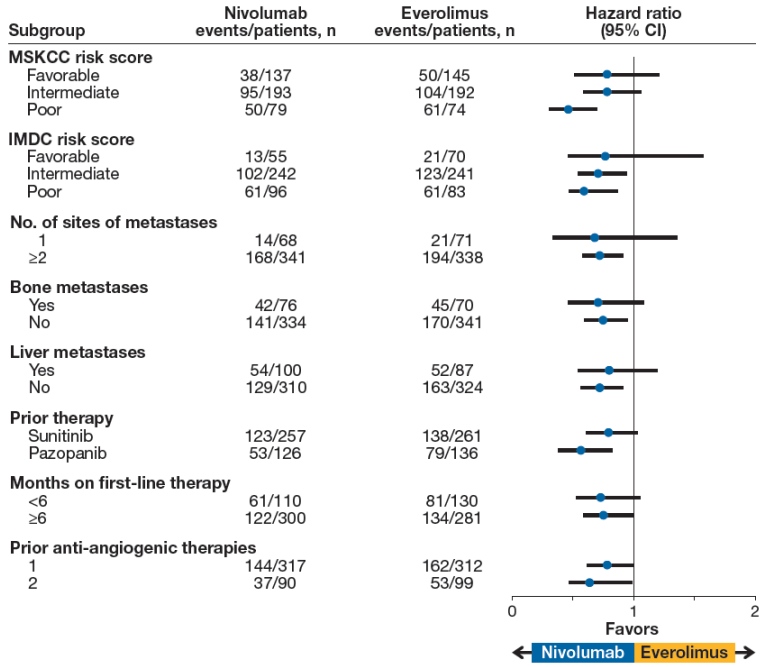
Abbreviations in table: CFB, change from baseline; EQ-5D, EuroQol-5 dimension.
Notes: [a]between-group comparison for median change from baseline

4.3.5 Subgroup analyses

Pre-planned subgroup analyses of CheckMate 025 (Figure 10) showed statistically significant differences in OS between nivolumab and everolimus treated patients who have had one previous anti-angiogenic therapy (HR 0.71, 95% CI: 0.56 to 0.90), MSKCC intermediate (HR 0.76, 95% CI:

0.58 to 0.99) and poor risk scores (HR 0.47, 95% CI: 0.30 to 0.73), male (HR 0.73, 95% CI: 0.58 to 0.92) and aged ≥65 to <75 years (HR 0.64, 95% CI: 0.45 to 0.91).[37]

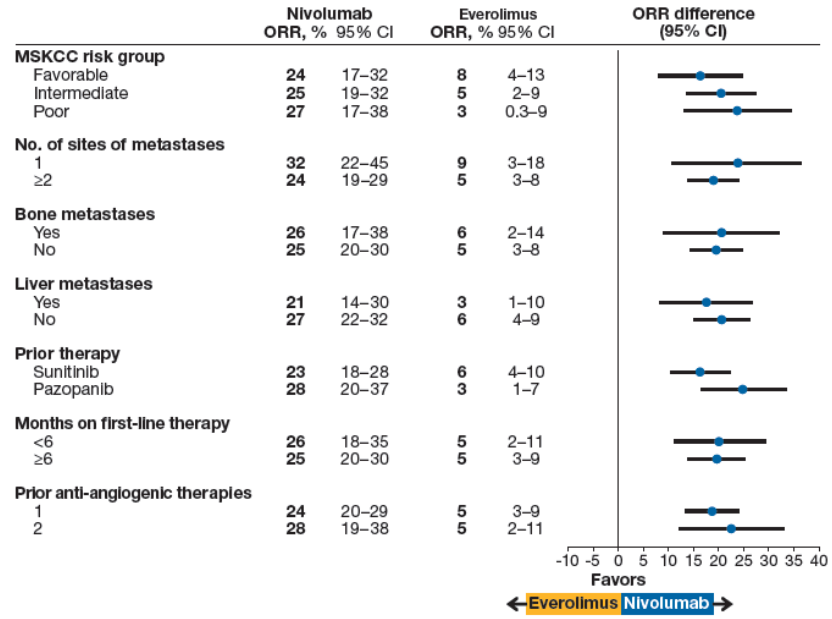
Figure 10. Forest plot of treatment effect on OS in pre-planned subgroups (reproduced from CS, pg 80, Figure 14, Section 4.7)



Abbreviations in figure: CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Centre; OS, overall survival.

Subgroup analysis of ORR also demonstrated statistically significant advantage with nivolumab treatment compared with everolimus (Figure 11).

Figure 11. Forest plot of treatment effect on ORR in pre-planned subgroups (reproduced from CS, pg 81, Figure 15, Section 4.7)



Abbreviations in figure: CI, confidence interval; Memorial Sloan Kettering Cancer Centre; ORR, objective response rate.

4.3.6 Adverse events

The company's summary of product characteristics (SmPC) (CS, Appendix 1, pg, 3-37) states, "Nivolumab is associated with immune-related adverse reactions. Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of nivolumab therapy". The SmPC also advises that nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life threatening immune-related adverse reaction.

The CS (pg 121–2, Section 4.12, Table 25) reports the incidence of select AEs (defined as AEs with potential immunological cause that is of special clinical interest with the use of nivolumab) in CheckMate 025.[37, 39] In the nivolumab group, reported select AEs with ≥5% incidence were skin (37.2%), gastrointestinal (GI) (24.4%), renal (17.5%) and hepatic (16%), while in the everolimus group they were GI (31.2%), pulmonary (18.6%) and skin (44.6%). However, the majority of the select AEs were transient, hence were readily manageable with either dose interruptions or administration of immune-modulating medications. Table 17 shows a summary of the incidence of select AEs in CheckMate 025.

Table 17. Summary of select AEs reported up to 30 days after last dose in CheckMate 025, all treated patients (reproduced from CS, pg 121, Section 4.12, Table 25)

Event	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	Treatment-related	All causality	Treatment-related
Endocrine	50 (12.3)	39 (9.6)	19 (4.8)	11 (2.8)
Grade 3-4	5 (1.2)	4 (1.0)	3 (0.8)	1 (0.3)
Time to onset, median weeks (range)	16.2 (2.1-91.0)	16.0 (2.1-61.0)	7.6 (3.1-69.3)	5.0 (3.1-40.1)
Resolution rate, n (%)	20 (40.0)	14 (35.9)	11 (57.9)	6 (54.5)
Time to resolution, median weeks (range)	Not reached (0.1-96.1+)	Not reached (1.9-96.1+)	27.9 (0.7-84.6+)	27.9 (0.7-79.4+)
Gastrointestinal	99 (24.4)	51 (12.6)	124 (31.2)	84 (21.2)
Grade 3-4	8 (2.0)	8 (2.0)	6 (1.5)	5 (1.3)
Time to onset, median weeks (range)	10.7 (0.1-83.0)	8.3 (0.1-83.0)	4.4 (0.1-68.1)	3.9 (0.1-64.4)
Resolution rate, n (%)	87 (87.9)	44 (86.3)	99 (81.1)	70 (85.4)
Time to resolution, median weeks (range)	4.1 (0.1-99.9+)	5.6 (0.1-88.3+)	4.9 (0.1-98.1+)	5.3 (0.1-98.1+)
Hepatic	65 (16.0)	46 (11.3)	45 (11.3)	28 (7.1)
Grade 3-4	19 (4.7)	11 (2.7)	4 (1.0)	2 (0.5)
Time to onset, median weeks (range)	8.0 (0.1-88.0)	7.2 (0.1-81.1)	4.4 (0.1-104.0)	4.1 (1.0-38.6)
Resolution rate, n (%)	54 (84.4)	37 (82.2)	32 (71.1)	24 (85.7)
Time to resolution, median weeks (range)	6.7 (0.9+-82.6+)	8.0 (1.6-82.6+)	9.9 (0.7-114.1+)	8.1 (0.9-99.7+)
Pulmonary	23 (5.7)	18 (4.4)	74 (18.6)	70 (17.6)

Event	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	Treatment-related	All causality	Treatment-related
Grade 3-4	6 (1.5)	6 (1.5)	15 (3.8)	13 (3.3)
Time to onset, median weeks (range)	17.7 (0.3-73.0)	16.6 (1.9-73.0)	12.6 (1.7-102.1)	13.7 (2.6-102.1)
Resolution rate, n (%)	18 (78.3)	15 (83.3)	60 (81.1)	56 (80.0)
Time to resolution, median weeks (range)	8.1 (1.3-68.7+)	5.6 (1.3-53.1+)	8.3 (0.4-101.0+)	8.3 (0.4-101.0+)
Renal	71 (17.5)	28 (6.9)	56 (14.1)	35 (8.8)
Grade 3-4	12 (3.0)	4 (1.0)	6 (1.5)	2 (0.5)
Time to onset, median weeks (range)	10.7 (0.1-79.1)	10.6 (4.0-79.1)	6.4 (0.1-69.1)	6.9 (1.4-69.1)
Resolution rate, n (%)	46 (65.7)	16 (59.3)	29 (52.7)	23 (65.7)
Time to resolution, median weeks (range)	8.1 (0.1-115.3+)	31.1 (0.6-77.1+)	26.1 (0.3+-102.3+)	12.7 (0.4-83.3+)
Skin	151 (37.2)	101 (24.9)	177 (44.6)	153 (38.5)
Grade 3-4	6 (1.5)	4 (1.0)	5 (1.3)	5 (1.3)
Time to onset, median weeks (range)	8.7 (0.1-75.0)	8.3 (0.1-75.0)	3.1 (0.1-78.1)	2.9 (0.1-69.4)
Resolution rate, n (%)	106 (71.6)	75 (75.8)	133 (75.1)	126 (82.4)
Time to resolution, median weeks	20.1 (0.1-113.7+)	20.1 (0.6-113.7+)	14.7 (0.1-113.9+)	10.9 (0.1-113.9+)
Hypersensitivity/ Infusion reactions	25 (6.2)	21 (5.2)	4 (1.0)	1 (0.3)
Grade 3-4	1 (0.2)	1 (0.2)	0	0
Time to onset, median weeks (range)	6.3 (0.1-120.1)	2.0 (0.1-96.9)	19.6 (0.4-24.1)	0.4
Resolution rate, n (%)	24 (96.0)	21 (100)	3 (75.0)	1 (100)
Time to resolution, median weeks (range)	0.1 (0.1-19.1)	0.1 (0.1-19.1)	0.4 (0.3-22.4+)	0.4
Abbreviations in table: AE, adverse event; CSR, clinical study report.				

The company reported that more patients in the everolimus group experienced at least one treatment-related adverse event (TRAE) (nivolumab [78.6%] vs everolimus [87.9%]), grade 3–4 TRAEs (nivolumab [19%] vs everolimus [37%]) and discontinuations due to TRAEs (nivolumab [7.6%] vs everolimus [13.1%]) compared to the nivolumab group in CheckMate 025 (CS, pg 117, Section 4.12, Table 23). The incidence of serious adverse events (SAEs), as well as treatment-related SAEs (TRSAEs) were similar in both nivolumab and everolimus groups. Table 18 is a summary of the safety profile of patients in CheckMate 025.

Table 18 .Summary of safety data from CheckMate 025, all treated patients (reproduced from CS, pg 117, Section 4.12, Table 23)

	Nivolumab (n=406)	Everolimus (n=397)
All AEs, n (%)	397 (97.8)	386 (97.2)
Grade 3-4 AEs, n (%)	216 (53.2)	224 (56.4)

TRAEs, n (%)	319 (78.6)	349 (87.9)
Grade 3-4 TRAEs, n (%)	76 (19)	145 (37)
All SAEs, n (%)	194 (47.8)	173 (43.6)
TRSAEs, n (%)	47 (11.6)	53 (13.4)
DC due to AEs, n (%)	72 (17.7)	82 (20.7)
DC due to TRAEs, n (%)	31 (7.6)	52 (13.1)
DC due to Grade 3–4 TRAEs, n (%)	19 (4.7)	28 (7.1)
Deaths relating to study drug, n (%)	0	2 (0.5)

Abbreviations in table: AE, adverse event; DC, discontinuation; SAE, serious adverse event; TRAE, treatment related adverse event; TRSAE, treatment related serious adverse event

In both CheckMate 010 and CheckMate 003 (as in CheckMate 025), the most commonly reported TRAE was fatigue. Reported incidence of fatigue in CheckMate 010[65] was 24% in nivolumab 0.3 mg/kg, 22% in nivolumab 2 mg/kg, and 35% in nivolumab 10 mg/kg groups; while in CheckMate 003, the incidence was 41% in patients with advanced RCC treated with nivolumab (regardless of dose.[65, 66]

In addition, discontinuations due to TRAEs were >10% in both CheckMate 010 and CheckMate 003; and most importantly no deaths were reported due to nivolumab toxicity in CheckMate 010 or in advanced RCC patients in CheckMate 003.

4.3.7 Meta-analysis

The company did not perform a meta-analysis as only as single RCT was identified comparing nivolumab with a comparator of interest (i.e. CheckMate 025[37], which compared nivolumab and everolimus). The company therefore conducted a network meta-analysis (NMA) to estimate the comparative efficacy of nivolumab with the other comparators outlined in NICE final scope[23] (i.e. axitinib and BSC).

4.4 Critique of trials identified and included in the indirect comparison and/or network meta-analysis

As a result of the lack of direct evidence for nivolumab compared to axitinib or BSC, as required by the NICE final scope[23], the company conducted a NMA. The ERG is concerned about attempting an NMA using CheckMate 025[37] as the basis for the effectiveness of nivolumab, since proportional hazards do not hold for PFS and for the initial period of OS. Issues with the proportional hazards assumption within CheckMate 025[37] have been discussed previously in Section 4.3.1 and Section 4.3.2. This will also be discussed in the summary of the NMA in Section 4.4.5.

4.4.1 NMA methods and assumptions

According to the CS (pg 94-5, Section 4.10.3), the NMA was conducted using the R package 'netmeta'[74] which utilises graph theoretical methods in a frequentist framework to analyse data from

treatment networks.[75] The results of the NMA have been reported using the fixed effect model. The company noted this limitation was due to only one trial being available for each link in the network (i.e. only one trial was available comparing each pair of treatments). As such, it was not possible to investigate statistical heterogeneity within the network. The ERG considers this approach to be reasonable.

The NMA was conducted on the log-hazard ratio scale, which is a relative measure of treatment efficacy. According to the CS (pg 94, Section 4.10.3), "The key assumption of this analysis is that of intra-trial proportional hazards; survival curves do not cross and are related to each other through a constant, time invariant, exponent. Use of this relative measure of treatment efficacy avoids the need for patients recruited to different trials within the network to have, on average, the same prognosis, e.g. if there are multiple placebo arms in a trial, these patients do not have to show the same median overall survival". The ERG agrees that this is a common assumption in meta-analysis and by extension NMA.

The company provides result for PFS and OS as it considers these two outcomes to represent key outcomes of interest to clinicians and patients, and they are also major drivers in the health economic model. The ERG considers this to be reasonable given the limited trial data available.

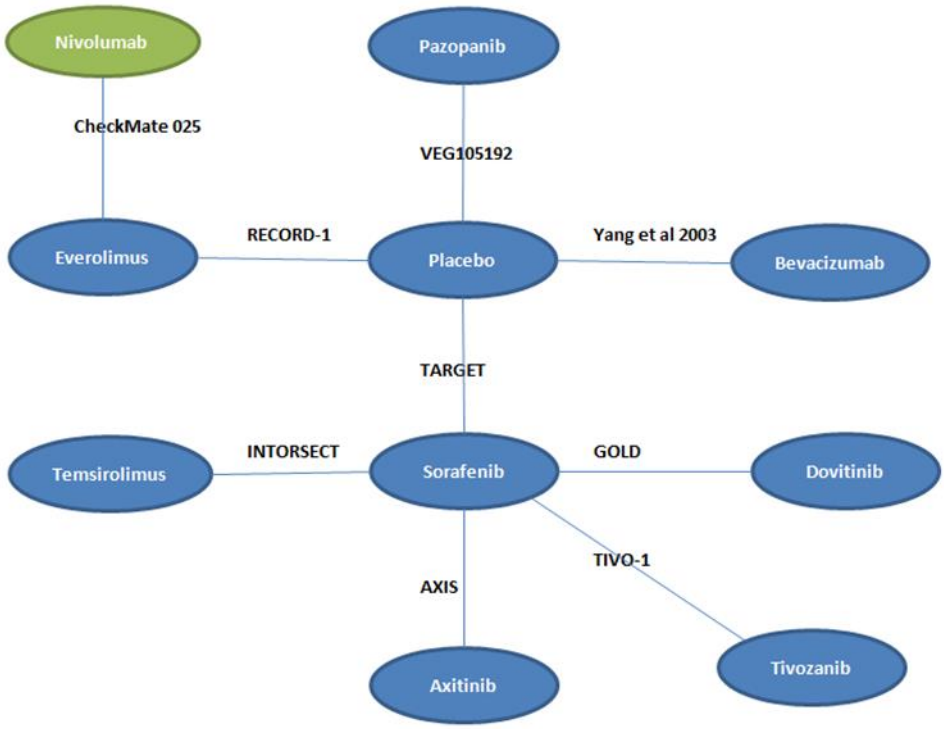
The company used two different data sets for the NMA: the first used the ITT hazard ratios (HR) for each of the trials (irrespective of subsequent treatment received), while the second used HRs that were crossover adjusted/crossover free. However, the latter approach was deemed by the company to be the most appropriate for the subsequent economic evaluation. While the ERG agrees that having similar data sets from all included trials is a key component of an NMA, the ERG disagrees that this was the case in the company's preferred analysis. This issue will be explored in Section 4.4.2 and discussed in Section 4.4.5.

4.4.2 Included studies in the NMA

As shown in Section 4.1.2 and Table 3 of this report, out of 21 studies that met the inclusion criteria for the systematic review, 18 RCTs were connected in an evidence network, and nine studies were included in the final NMA. The company's states the, "The primary reason for study exclusion from the NMA was small sample size and/or limited data availability due to study results only being available from conference abstracts at the time of assessment".

The ERG does not agree that sample size alone is a valid criterion for excluding trials from an NMA. A potentially valid reason for excluding Ratain *et al.* 2006[54] (comparing sorafenib with placebo), which was excluded due to small sample size, would have been its limited reporting of PFS (only in weeks) without OS.

Figure 12. Network diagram for OS and PFS (adapted from CS, pg 94, Figure 17, Section 4.10.2)



Notes: Data from the TIVO-1 trial is included in the synthesis of PFS but not OS (represented by green dotted line).

As shown in Figure 12, the company included other comparators outside NICE final scope,[23] and as stated in Section 4.1.1 of this report, the company's explanation was that the search was part of a global search and was not limited to this STA. The ERG notes that extending the network to include treatments that are not considered in the NICE final scope[23] makes no difference to the estimates calculated in the NMA from a more simplistic "linear" network including only those trial connecting nivolumab with axitinib (i.e. CheckMate 025[37], RECORD-1[55], TARGET[58], and AXIS[45]). As such, the ERG will limit its critique of studies included into the network to those that affect the comparison of nivolumab with axitinib and BSC.

The ERG notes the use of placebo from two trials included in the network (TARGET[58] and RECORD-1[55]) was assumed as proxy for BSC. Although no explanation/rationale was provided in the CS, the ERG is aware that this is a standard approach.[76]

As shown in Table 19, the ERG would like to highlight the lack of comparability of the trials included in the NMA due to differences in prior treatment (e.g. cytokines, vascular endothelial growth factor [VEGF]-targeted therapy, etc.) and line of treatment. The company uses the subgroup of patients in AXIS[45] who have had prior treatment with sunitinib, as axitinib is the only treatment recommended by NICE for patients with advanced/metastatic RCC who have had previous anti-angiogenic therapy. However, if prior treatment does impact on the benefit received from subsequent treatments, the ERG

is concerned about the potential imbalance in previous treatments in the studies included in the network.

In addition, while three studies were purely 2nd-line (AXIS[45], RECORD-1[55], TARGET[58]), CheckMate 025[37] was 2nd and post-2nd -line. However, this may have had limited impact on the network since the subgroup analysis of OS in CheckMate 025[37] (Figure 10), demonstrates no statistically significant difference in treatment effect between patients who have had one previous therapy (HR 0.71, 95% CI: 0.56 to 0.90) and patients who have had two previous therapies (HR 0.89, 95% CI: 0.61 to 1.29).[37]

Table 19. Previous systemic and line of treatments in trials contributing to NMA of OS and PFS

Trial name	Treatment arms	Previous treatment	Line of treatment
AXIS[45]	Axitinib vs sorafenib	Sunitinib, cytokines, bevacizumab, temsirolimus	Second-line
CheckMate 025[37]	Nivolumab vs everolimus	Sunitinib, pazopanib, axitinib	Second and post second-line
RECORD-1[55]	Everolimus plus BSC vs placebo plus BSC	Sunitinib, sorafenib, cytokines interferon, interleukin-2, bevacizumab	Second-line
TARGET[58]	Sorafenib vs placebo	Cytokines (interferon, interleukin-2)	Second-line
Abbreviations in table: BSC, best supportive care.			

The ERG also notes that the prognosis (MSKCC risk scores) of patients in CheckMate 025[37, 39] at baseline was better than patients in AXIS as shown in Table 20. The proportion of patients with favourable and intermediate MSKCC risk scores in CheckMate 025 was higher than in AXIS.

Table 20. Comparison of MSKCC risk groups in CheckMate 025 and AXIS

MSKCC risk group, n (%)	CheckMate 025[37, 39]		AXIS[45]	
	Nivolumab (n=410)	Everolimus (n=411)	Axitinib (n=361)	Sorafenib (n=362)
Favourable	145 (35%)	148 (36%)	100 (28%)	101 (28%)
Intermediate	201 (49%)	203 (49%)	134 (37%)	130 (36%)
Poor	64 (16%)	60 (15%)	118 (33%)	120 (33%)
Abbreviations in table: MSKCC, Memorial Sloan Kettering Cancer Center. Sources: CheckMate 025[37, 39]; AXIS [45]				

4.4.3 Data used in the NMA

Table 21 summarises the trial results (ITT and crossover adjusted) contributing to the NMA for OS and Table 22 summarises the ITT results of trials contributing to the NMA for PFS.

Table 21. Summary of trial results contributing to the NMA for OS (reproduced from CS, pg 97, Section 4.10.4)

Trial name	Test	Control	ITT HR [95% CI][a] (OS)	Crossover adjusted/free HR [95% CI] (OS)
CheckMate 025[37]	Nivolumab	Everolimus	0.73 [0.57, 0.93][b]	NA
AXIS[45]	Axitinib	Sorafenib	1.00 [0.78, 1.27][c]	NA
RECORD-1[55]	Everolimus	Placebo	0.87 [0.65,1.17]	0.60 [0.22,1.65][d(77)]
TARGET[58]	Sorafenib	Placebo	0.88 [0.74, 1.04]	0.72 [0.54, 0.94][e(58)]

Abbreviations in table: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.
Notes: [a]data presented to two decimal places; [b]98.5% has been reported in line with the results of the primary analysis; [c]prior sunitinib subgroup data; [d]IPCW estimate; [e]crossover free estimate. Hazard ratios obtained using digitisation of survival curves.

The ERG notes that crossover adjusted estimates have been provided for RECORD-1[77] and TARGET[58]. However, the methodology employed to estimate the "crossover adjusted/free" results has not been assessed by the company as to whether it is/isn't an appropriate methodology to employ. The ERG considers it likely that the company has made use of published data without carrying out this level of scrutiny. Of particular concern are the results used from AXIS[45]; when Motzer *et al.* report the overall survival results they highlight that, "Analysis of overall survival might have been confounded by subsequent active treatments, which were given to the majority of patients who discontinued study treatment". [45] Given the company's concerns around the impact of crossover, and its use of crossover adjusted/free results for RECORD-1[77] and TARGET[58], the ERG does not understand why the issue of subsequent active treatments in AXIS was not mentioned and accounted for in the CS.

The ERG is also concerned about the immature OS results used from TARGET. [58] The company states (CS, pg 96, Section 4.10.4), "The TARGET trial permitted crossover from placebo to sorafenib following a statistically significant PFS being observed. Although, at this point, the OS data were relatively immature (220 deaths; 41% of the protocol defined 540 deaths had been observed), the estimation of survival was unbiased and there was a numerical advantage of sorafenib over placebo (HR 0.72, 95% CI: 0.54 to 0.94; p=0.02)". The impact of using immature survival on the results of the NMA will be discussed further in Section 4.4.5.

Table 22. Summary of trial results contributing to the NMA for PFS (reproduced from CS, pg 99, Section 4.10.5)

Trial name	Test	Control	ITT HR [95% CI]* (OS)	Independent review or investigator assessed PFS
CheckMate 025[37]	Nivolumab	Everolimus	0.88 [0.75, 1.03]	Investigator assessed
AXIS[45]	Axitinib	Sorafenib	0.74 [0.57, 0.96]	Investigator assessed
RECORD-1[55]	Everolimus	Placebo	0.33 [0.25,0.43]	Independent review
TARGET[58]	Sorafenib	Placebo	0.51 [0.43, 0.60]	Investigator assessed

Abbreviations in table: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.
Notes: *Data presented to two decimal places. Hazard ratios obtained using digitisation of survival curves.

As shown in Table 22, the assessment of PFS was not consistently assessed in all four trials included in the network. Independent review is likely to be the least biases method of assessment but the ERG appreciates that it was beyond the control of the company to obtain a consistent data set. However, this potential bias introduced was not discussed in the CS. In addition, as mentioned in Section 4.4.2, the ERG is concerned about the potential influence prior treatment may have had on the comparability of response in the four trials.

4.4.4 NMA results

As shown in Figure 13, in the ITT analysis, [redacted]

Figure 13. NMA results for OS, HRs for nivolumab versus comparators (ITT results) (CS, pg 101, Figure 18a, Section 4.10.6)

Abbreviations in figure: BID, twice daily; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OD, once daily; Q2W, every 2 weeks

In the crossover-adjusted analysis, as shown in Figure 14, [redacted]

Figure 14. NMA results for OS, HRs for nivolumab versus comparators (crossover adjusted results) (CS, pg 101, Figure 18b, Section 4.10.6)

Abbreviations in figure: BID, twice daily; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OD, once daily; Q2W, every 2 weeks.

[redacted] (Figure 15) [redacted] (Figure 16).

Figure 15. NMA results for OS, HRs for everolimus versus comparators (ITT results) (CS, pg 105, Figure 1a, Appendix 7, Section 4.10)

Abbreviations in figure: BID, twice daily; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OD, once daily; Q2W, every 2 weeks

Figure 16. NMA results for OS, HRs for everolimus versus comparators (crossover adjusted results) (CS, pg 105, Figure 1b, Appendix 7, Section 4.10)

Abbreviations in figure: BID, twice daily; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OD, once daily; Q2W, every 2 weeks

In the ITT analysis as shown in Figure 17,

Figure 17. NMA results for PFS, HRs of nivolumab versus comparators (ITT) analysis (CS, pg 102, Fgure 19A, Section 4.10.6)

Abbreviations in figure: BID, twice daily; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OD, once daily; Q2W, every 2 weeks

The ERG notes

4.4.5 Discussion of the NMA

The ERG considers that the company's NMA may be fundamentally flawed and producing biased estimates of treatment effects. These will be outlined below with the ERG's view on the potential impact of each limitation:

- Non-proportional hazards – as mentioned in Section 4.4 (and discussed in more detail in Section 4.3.1 and Section 4.3.2), proportional hazard do not hold within CheckMate 025[37] for PFS and, at least not initially, for OS. This means that any estimated HRs using nivolumab as a baseline are likely to be misleading. However, as proportional hazards may hold for the rest of the network, using everolimus as a baseline may be a reasonable compromise assuming a different approach is used for integrating the results of nivolumab. This is the approach the company takes for PFS but not for OS. The ERG considers assuming proportional hazards for OS may be a pragmatic simplification but the potential impact of this, in particular with respect to the results of the economic evaluation, should have been highlighted in the CS. Issues regarding the use of PFS and OS in the economic evaluation are discussed in more detail in Section 5.4.2.

- OS adjustments for crossover – the lack of accounting (or even acknowledging) the impact of subsequent active treatments in AXIS is highly likely to bias the estimated treatment effect for OS. In the presence of crossover, differences in OS are likely to be minimised.

- Immature OS for TARGET – if it is assumed that sorafenib is likely to be more effective than placebo; utilising immature survival data is likely to underestimate the benefit of sorafenib over placebo. While the ERG appreciates that the company was attempting to use crossover free results, the likely impact of this should have been explicitly stated as a limitation and the potential direction of bias acknowledged.

- The impact of not adjusting for subsequent active treatments in AXIS and not using mature and crossover-free OS data for TARGET is likely to minimise any relative benefit for axitinib compared to sorafenib in the network.

- Differences in prior treatment – while the ERG is unable to assess the impact of differences in prior treatments, it seems likely that this will make a difference in the estimated PFS and OS for trials included in the network.

The ERG's clinical experts were surprised to see a numerical benefit in OS for everolimus over axitinib as this was not their experience in clinical practice. The ERG's clinical experts considered axitinib to be more effective than everolimus but, as a conservative estimate, didn't consider it unreasonable that they might have similar efficacy. In addition, the CS (pg 144, Section 5.3.1) states that, "At clinical review, oncologists did not anticipate a survival advantage of everolimus over axitinib".

Overall, the ERG considers the company's NMA to produce results for OS that may be flawed. Setting aside the initial period where proportional hazards do not hold in CheckMate 025, the nature

of the differences in the data used seems likely to underestimate the benefit of axitinib for OS. The ERG considers the company's NMA to be unreliable for generating reliable estimates of PFS compared to nivolumab. While this has been mitigated to a degree by using everolimus as a baseline, the potential impact of prior treatments may invalidate the estimates for everolimus compared with axitinib. Based on clinical expert feedback, and the non-significant results from the company's NMA, the ERG considers using the everolimus treatment group in CheckMate 025 to be the best available surrogate for axitinib for a comparison with nivolumab. While there are issues with the comparison with BSC, these are likely to have less impact primarily due to mature crossover-adjusted OS being available from RECORD-1 for a direct comparison of everolimus and BSC.

4.4.6 Qualitative synthesis of adverse events in CheckMate 025 and AXIS

In a qualitative synthesis of adverse events in CheckMate 025[37, 39] and AXIS,[45] the company reports (CS, pg 123–4, Section 4.12) a safety advantage of nivolumab versus axitinib as observed in nivolumab versus everolimus in CheckMate 025 in TRAEs with ≥10% incidence. As observed in Table 23, the incidence (≥10%) of TRAEs of diarrhoea, hypertension, decreased appetite, nausea, dysphonia, hand-foot syndrome, hypothyroidism, weight decrease, asthenia, vomiting, mucosal inflammation, stomatitis and proteinuria were higher with axitinib than with nivolumab.

However, as noted by the ERG's clinical experts, there is a lack of comparability of baseline characteristics of CheckMate 025 and AXIS. While AXIS was a purely second-line treatment trial, CheckMate 025 was second-line and post second-line treatment trial. In addition, patients in CheckMate 025 had better prognosis than AXIS (higher proportion of patients with favourable and intermediate MSKCC risk scores in CheckMate 025 was higher than in AXIS).

Table 23. Summary of TRAEs (≥10%) from axitinib arm of AXIS and nivolumab arm of CheckMate 025 (reproduced from CS, pg 124, Section 4.12, Table 26)

Event	Axitinib (n=359), n (%)		Nivolumab (n=406), n (%)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhoea	193 (53.8)	40 (11.1)	50 (12.3)	5 (1.2)
Hypertension	149 (41.5)	60 (16.7)	6 (1.5)	3 (0.7)
Fatigue	133 (37.0)	37 (10.3)	134 (33.0)	10 (2.5)
Decreased appetite	113 (31.5)	15 (4.2)	48 (11.8)	2 (0.5)
Nausea	109 (30.4)	6 (1.7)	57 (14.0)	1 (0.2)
Dysphonia	102 (28.4)	0	7 (1.7)	0
Hand-foot syndrome	100 (27.9)	20 (5.6)	-	-
Hypothyroidism	72 (20.1)	1 (<0.5)	24 (5.9)	1 (0.2)
Weight decreased	70 (19.5)	12 (3.3)	19 (4.7)	1 (0.2)
Asthenia	66 (18.4)	15 (4.2)	18 (4.4)	1 (0.2)
Vomiting	63 (17.5)	5 (1.4)	24 (5.9)	0
Mucosal inflammation	58 (16.2)	5 (1.4)	11 (2.7)	0

Event	Axitinib (n=359), n (%)		Nivolumab (n=406), n (%)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Stomatitis	55 (15.3)	5 (1.4)	8 (2.0)	0
Rash	47 (13.1)	1 (<0.5)	41 (10.1)	2 (0.5)
Constipation	45 (12.5)	1 (<0.5)	24 (5.9)	1 (0.2)
Proteinuria	45 (12.5)	11 (3.1)	1 (0.2)	0
Dysgeusia	41 (11.4)	0	11 (2.7)	0
Headache	39 (10.9)	3 (0.8)	24 (5.9)	0
Arthralgia	36 (10.0)	3 (0.8)	27 (6.7)	1 (0.2)
Dry skin	36 (10.0)	0	26 (6.4)	0
Pruritus	22 (6.1)	0	57 (14.0)	1 (0.2)
Notes: [a]this is not intended as a cross-trial comparison because of drawbacks of differences in trial design.				

4.5 Conclusions of the clinical effectiveness section

- Nivolumab has currently not been granted marketing authorisation in England for the treatment of RCC. However, the Committee for Medical Products for Human Use (CHMP) gave a positive opinion on nivolumab on 25th February 2016;

- The primary objective of CheckMate 025,[37, 39] was to compare the safety and efficacy of nivolumab with everolimus in patients with advanced RCC previously treated with anti-angiogenic therapy. Other inclusion criteria were: adults (aged ≥18 years); measurable disease according to RECIST criteria v1.1; received no more than three total previous regimens of systemic therapy; disease progression during or after the last treatment regimen and within 6 months before study enrolment; and with Karnofsky performance status of ≥70%;

- The primary outcome of CheckMate 025 was OS. Median OS in CheckMate 025 was significantly longer in nivolumab treated patients (25.0 months, 95% CI: 21.8 to not estimable) compared with everolimus treated patients (19.6 months, 95% CI: 17.6 to 23.1), (HR 25, 95% CI: 21.8 to not estimable);

- Median PFS in CheckMate 025 was not statistically significantly different between nivolumab and everolimus groups (4.6 months, 95% CI: 3.7 to 5.4 vs 4.4 months, 95% CI: 3.7 to 5.5, respectively; HR 0.88, 95% CI: 0.75 to 1.03, p=0.11);

- ORR in CheckMate 025 was significantly higher in the nivolumab compared with the everolimus group (25% vs 5%, respectively) (OR: 5.98; 95% CI: 3.68 to 9.72; p<0.001);

- HRQoL (FKSI-DRS) in CheckMate 025 significantly improved in the nivolumab group compared with the everolimus group after one year, and a higher proportion of patients in the

nivolumab group experienced meaningful improvement in FKSI-DRS compared with the everolimus group (55% vs 37%, respectively; p<0.001);

- Pre-planned subgroup analyses of CheckMate 025 showed statistically significant differences between nivolumab and everolimus treated patients who have had one previous anti-angiogenic therapy (HR 0.71, 95% CI: 0.56, 0.90), MSKCC intermediate (HR 0.76, 95% CI: 0.58 to 0.99) and poor (HR 0.47, 95% CI: 0.30 to 0.73), male (HR 0.73, 95% CI: 0.58 to 0.92) and aged ≥65 to <75 years (HR 0.64, 95% CI: 0.45 to 0.91);

- MSKCC risk group, number of prior anti-angiogenic therapies, age, type and duration of prior therapy, number and site of metastases generally showed greater OS and ORR in the nivolumab group compared with the everolimus group;

- The incidence of select AEs with ≥5% incidence in CheckMate 025 in the nivolumab group were skin (37.2%), GI (24.4%), renal (17.5%) and hepatic (16%), while in the everolimus group they were GI (31.2%), pulmonary (18.6%) and skin (44.6%);

- CheckMate 010,[65] a randomised dose ranging trial and CheckMate 003,[66] a randomised dose escalation trial provided data to support CheckMate 025;

- In the NMA, the ITT analysis of OS indicated that [redacted];

- In the NMA, [redacted]

- The results of the NMA should be interpreted with caution due to the lack of baseline comparability of the included trials (differences and number of prior treatments, and MSKCC risk scores). In addition, there is lack of quality OS RCT data available due to high levels of crossover and/or immaturity of the existing data;

- Nivolumab did not show a curative effect in CheckMate 025, and the reasons provided by the company included insufficient follow-up and/or sample size not powered enough to detect such an effect. However, the ERG's clinical experts are of the view that it may also be due to the mechanism of action of nivolumab. It takes time for the host response to be engaged with immunotherapies such as nivolumab whereas targeted agents such as everolimus exert their effect more rapidly. Potentially immunotherapies may achieve a plateau at a higher survival rate than targeted agents or chemotherapy, as demonstrated by the use of ipilimumab in melanoma.[72]

4.5.1 Clinical issues

- Axitinib is the only recommended treatment for second-line advanced/metastatic RCC by NICE in England. However, there is no direct RCT data comparing nivolumab with axitinib. The pivotal trial in the CS (CheckMate 025) compared nivolumab with everolimus. Nivolumab was therefore compared with axitinib in the CS through an NMA involving trials with potentially dissimilar baseline characteristics in terms of prior treatment (cytokines and/or VEGF-targeted therapy or systemic treatment-naive) and number of prior treatment and prognostic risk scores;

- According to the ERG's clinical experts, while nivolumab may be considered well tolerated by patients, the immunotherapy-related side effects are different to what clinicians usually encounter with current treatments for RCC. Therefore, there will be the need for training of clinicians to assess and manage immunotherapy-related complications.

5 COST EFFECTIVENESS

5.1 Introduction

This Section provides a structured description and critique of the *de novo* economic evaluation submitted by the company for nivolumab for previously treated advanced or metastatic renal cell carcinoma (RCC).

The company provided a written submission of the economic evidence along with an electronic version of the Microsoft® Excel®-based economic model. Table 24 summarises the location of the key economic information within the company's submission (CS).

Table 24. Summary of key information within the company's submission

Information	Section (CS)
Details of the review of the economic literature	5.1
Model structure	5.2.2
Technology	5.2.3
Clinical parameters and variables	5.3
Measurement and valuation of health effects and adverse events	5.4
Resource identification, valuation and measurement	5.5
Sensitivity analysis	5.8
Results	5.7
Validation	5.10
Subgroup analysis	5.9
Strengths and weaknesses of economic evaluation	5.11
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

The company presented the results of pairwise analysis of nivolumab compared to axitinib, everolimus and best supportive care (BSC). The base case and probabilistic results are presented in Table 25 and Table 26, respectively.

Table 25. Base case results of nivolumab versus comparators (CS, pg 191, Table 60)

Comparator	Costs	QALYs	LYG	Incremental, nivolumab versus comparator			ICER
				Costs	QALYs	LYG	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£46,133.83	1.25	2.09	£45,219	1.07	1.35	£42,417.26
Everolimus	£38,920.38	1.69	2.55	£52,432	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,828	1.43	1.97	£56,427.43
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 26. Mean results of probabilistic sensitivity analysis (adapted from CS, pg 204, Table 72)

Comparator	Costs	QALYs	LYG	Incremental, nivolumab versus comparator			ICER
				Costs	QALYs	LYG	
Nivolumab	£91,964	2.36	3.55				
Axitinib	£48,655	1.46	2.59	£43,310	0.90	0.96	£47,928
Everolimus	£39,127	1.72	2.62	£52,838	0.64	0.93	£82,288
BSC	£11,270	1.02	1.77	£80,694	1.34	1.78	£60,077

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

5.3 ERG comment on company's review of cost-effectiveness evidence

The company stated that, "an up-to-date systematic literature review of previous cost-effectiveness studies was not completed in time for this submission" (CS, pg 133, Section 5.1). The company referred to a systematic literature review performed in June 2012 for a previous technology appraisal (axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment, TA333)[78, 79] and stated that, "There is an established paradigm of Markov modelling with health states to capture the key clinical outcomes of disease progression and death, in previously treated, advanced RCC" (CS, pg 133, Section 5.1).

No other details from the systematic review of cost-effectiveness evidence performed for TA333 were reported.

5.4 Overview of company's economic evaluation

5.4.1 Model structure

In this Section, the ERG presents the model developed by the company. A detailed discussion and critique of the model structure and modelling approaches is included in Section 5.5.2 .

The company developed a *de novo* model in Microsoft Excel to assess the comparative cost-effectiveness of nivolumab in adults with previously treated advanced or metastatic renal cell carcinoma (RCC). The treatment options included in the model were nivolumab, everolimus, axitinib and best supportive care (BSC). An area-under the curve (AUC) approach was adopted for the analysis, modelling the proportions of patients in each health state based on parametric survival curves for each clinical outcome. Overall survival (OS) was used to determine how many patients were dead or alive; progression-free survival (PFS) to determine the proportions of alive patients who had progressed or not; and time-to-discontinuation (TTD) data were used to inform the number of patients who were on or off treatment.

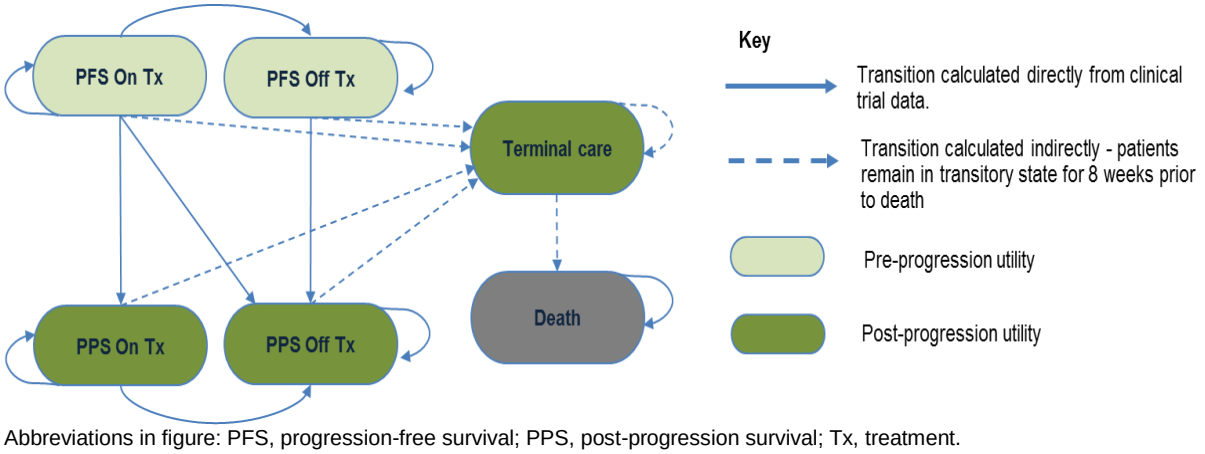
Patients in the CheckMate 025 trial could continue receiving treatment after disease progression, or discontinue treatment before disease progression.[37] Due to this, the company modelled progression status (pre and post-progression) and treatment status (on or off treatment) independently.

The model consisted of six health states, to reflect the clinical events experienced by patients and to capture resource use for treatment of advanced or metastatic RCC. The health states included in the model were:

- Progression-free survival (PFS), divided into:
    - Progression-free survival on treatment (PFST);
    - Progression-free survival off treatment (PFSN);
- Post-progression survival (PPS), divided into:
    - Post-progression survival on treatment (PPST);
    - Post-progression survival off treatment (PPSN);
- Terminal care (TC);
- Death.

Health-related quality of life (HRQoL) and resource use were expected to vary according to progression status, and were captured by the health states in the model. All patients entering the model were assumed progression-free and receiving treatment (i.e. in the PFST health state). Patients could only transition to the "death" health state through the "terminal care" tunnel state in which they were assumed to spend 8 weeks; no sudden deaths were assumed to occur in the model. The model structure used in the company's base case is presented in Figure 18.

Figure 18. Model structure (CS, pg 134, Figure 23)



Abbreviations in figure: PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

A lifetime horizon of 30 years was adopted, and time was discretised into weekly cycles. No half-cycle correction was applied due to the short length of the cycle. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects were discounted at annual rate of 3.5%, in line with the NICE Reference Case.[80]

5.4.2 Treatment effectiveness

In this Section the ERG presents an overview of the company's modelling strategy, the analyses performed on the CheckMate 025 trial and how the results from the head-to-head and indirect analyses were implemented in the economic model.

Treatment effectiveness was mainly determined by the patient time spent in each of the six health states of the model. An additional key factor related to treatment effectiveness was the treatment-specific HRQoL profile and the impact of treatment-related adverse events (TRAEs) on patients' HRQoL, discussed in 5.4.4.

Three trial outcomes were used in the model to determine where patients were in the model at each cycle, i.e. how patients were distributed in the six health states over time. These were:

- Overall survival (OS), determining the proportion of patients alive and dead. The increase in the proportion of patients in the death health state was used to calculate how many patients would receive terminal care in the previous model cycles;

- Progression-free survival (PFS), used to separate the patients in the alive and not progressed health state from the dead or progressed health state;

- Time to discontinuation (TTD), determining the proportions of patients who were on or off treatment.

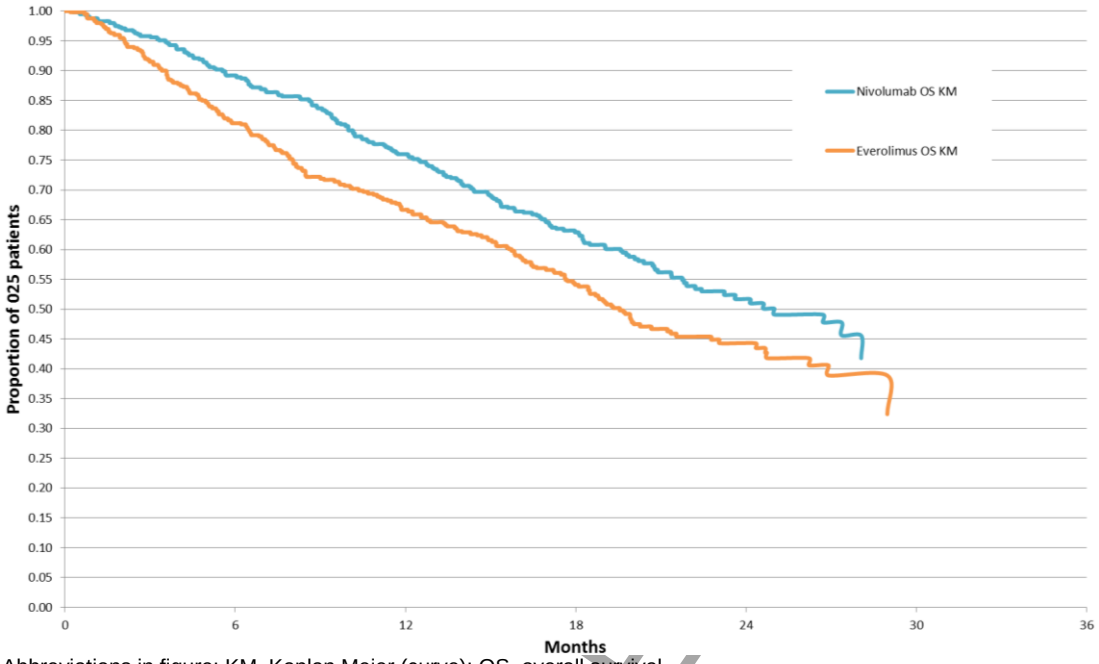
OS, PFS and TTD were analysed independently. The comparison between nivolumab and everolimus was informed by parametric survival analyses of OS, PFS and TTD data from the CheckMate 025 trial.[39] Hazard ratios (HRs) derived from the network meta-analysis (NMA) of PFS and OS, described in Section 4.4, were applied to the everolimus curve to estimate the proportions of patients in each health state over time for axitinib and best supportive case (BSC) under the assumption of proportional hazards.

The analyses for OS, PFS and TTD are described in Section 5.4.2.1, Section 5.4.2.2 and Section 5.4.2.3, respectively. The ERG's critique of the company's analyses is included in Section 5.5.5.

5.4.2.1 Overall survival

The Kaplan Meier (KM) curves for the OS observed in the CheckMate 025 trial for the nivolumab and everolimus arms are reported in Figure 19. The number of patients at risk over time in the trial are reported in Table 27. The ERG notes that the numbers of patients at risk reported by the company in Table 30 of the CS (and replicated in Table 27) did not correspond with the values included in the electronic model (not shown). However, the KM curves in the model were identical to the ones shown in Figure 24 of the CS (replicated in Figure 19).

Figure 19. KM OS data, CheckMate 025 (CS, pg 138, Figure 24)



Abbreviations in figure: KM, Kaplan Meier (curve); OS, overall survival.

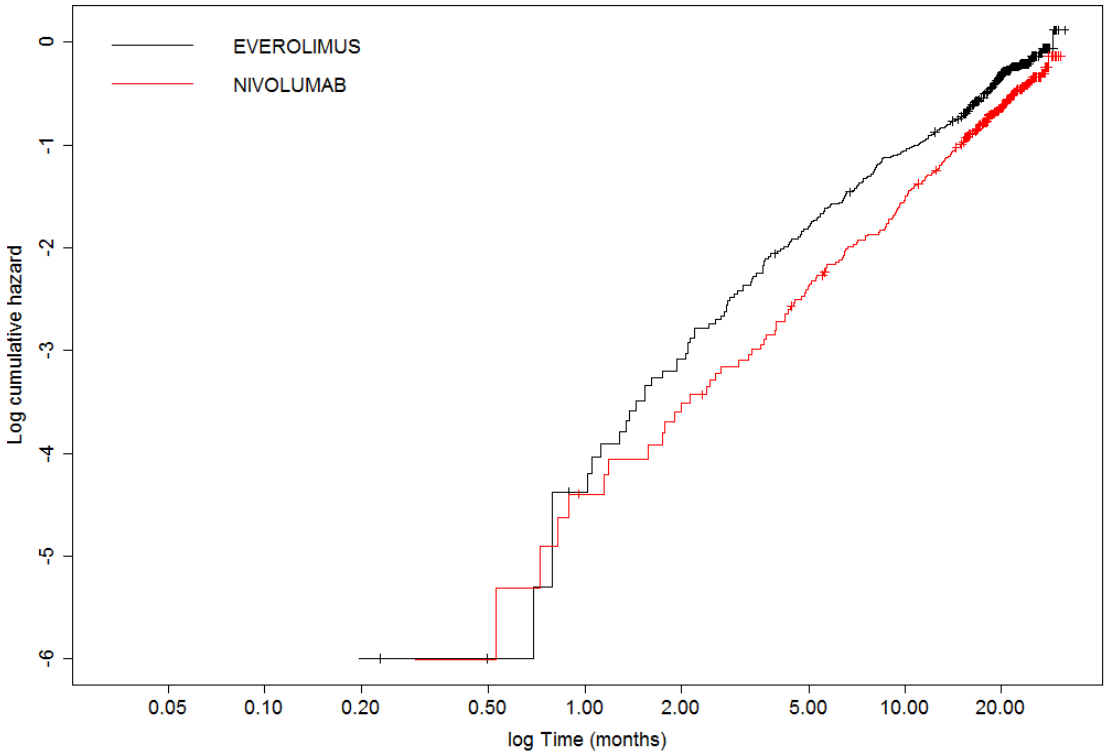
Table 27. Number at risk over time, overall survival, CheckMate 025 (CS, pg 138, Table 30)

Months	0	3	6	9	12	15	18	21	24	27	30	33
NAR - Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
NAR - Everolimus	411	366	324	287	265	241	187	115	61	20	2	0
Abbreviations in table: NAR, number at risk.												

The company reported that, "The assumption of proportional hazards (PH) in OS KM data was tested, to assess whether survival analysis stratified by treatment group was appropriate" (CS, pg 138, Section 5.3.1). The company considered the KM curves (Figure 19) and the log-cumulative hazard plot (Figure 20) to be suggestive of PH across treatment arms for the observed OS data in the CheckMate 025 RCT. The ERG notes that the cumulative hazard plot should show two curves separated by a distance that should remain constant over time under the PH assumption. The company concluded that survival analyses for the OS could be performed using non-stratified parametric models.

The ERG notes that the company did not report any further explanation on how the PH assumption was deemed to hold or why the two figures included would be sufficient to support it.

Figure 20. Log-cumulative hazard plot, OS in CheckMate 025 (CS, pg 139, Section 5.3.1)



Six parametric models were fitted to the non-stratified OS dataset: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. The company reported assessing the most appropriate distribution using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) statistics. In addition, "the plausibility of different extrapolations was assessed by visual inspection, by oncologists currently practising within the NHS in England and Wales, in three separate interviews" (CS, pg 139, Section 5.3.1). The AIC and BIC indexes resulting from the parametric analysis are reported in Table 28.

Table 28. AIC and BIC statistics, standard model fitst to un-stratified OS data from CheckMate 025 (adapted from CS, pg 142, Table 31)

Model	AIC	BIC
Log-logistic	3564.866	3578.998
Generalised gamma	3565.231	3584.073
Weibull	3567.777	3581.909
Log-normal	3567.653	3583.784
Gompertz	3574.170	3588.301
Exponential	3578.360	3587.781
Abbreviations in table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

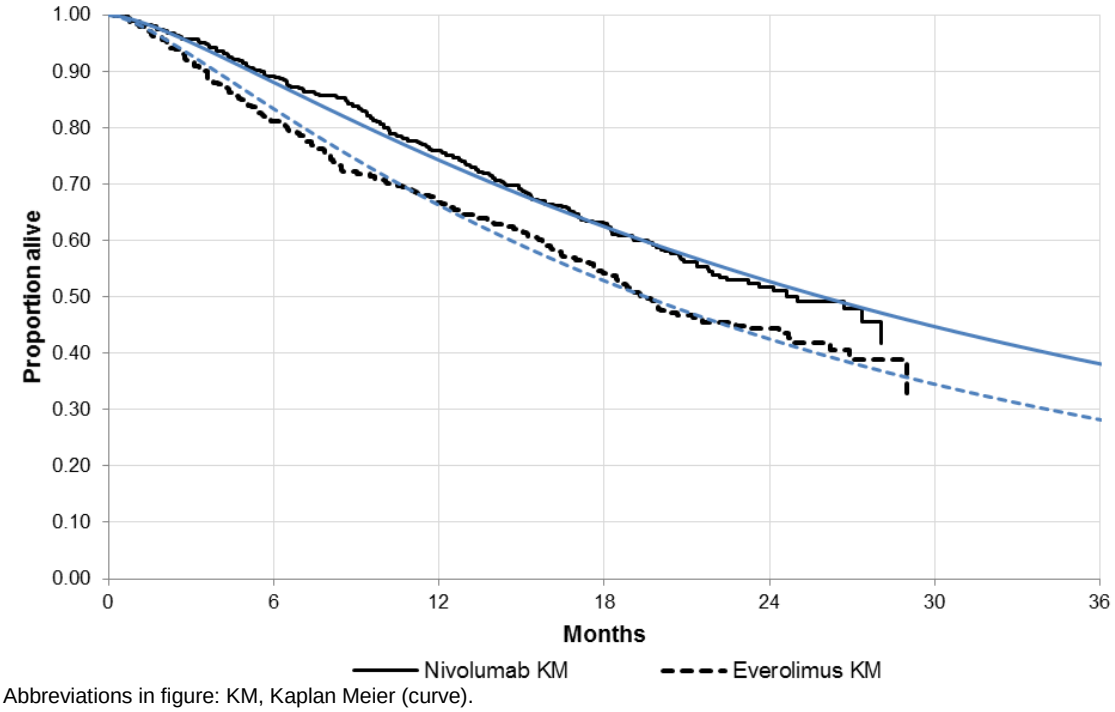
Even though the log-logistic curve reported the lowest AIC and BIC measures among the parametric curves tested, it was not selected as the base case model. This was because the extrapolated survival based on the log-logistic model for everolimus was not considered a reasonable estimate by clinical experts. The best-fitting curve among the ones predicting a survival in line with the experts' estimates was the generalised gamma model. The company's justification is reported in Box 4.

Box 4. Company's justification for the use of the generalised gamma model for the OS (CS, pg 140, Section 5.3.1)

To validate extrapolation assumptions, clinicians were shown the log-logistic curve fit to the everolimus data, with the rationale that their experience of patients with this established treatment was greater than their experience of long-term survival for nivolumab patients. They were then asked if this matched their expectations for previously treated patients who receive everolimus, with reference to predicted 5-year survival of around 17.5% from the best fitting model according to AIC and BIC […], the log-logistic model. Oncologists independently reported that the log-logistic extrapolations were too optimistic and independently estimated that expected 5-year survival for such patients treated with everolimus is realistically around 10-12%. […] Owing to the importance of clinical plausibility when extrapolating beyond observed data, the generalised gamma model, which provides a better statistical fit to the KM data than the exponential model, is used in the base case.
Abbreviations in box: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan Meier; OS, overall survival.

A comparison between the estimated generalised gamma curve and the CheckMate 025 OS data is reported in Figure 21.

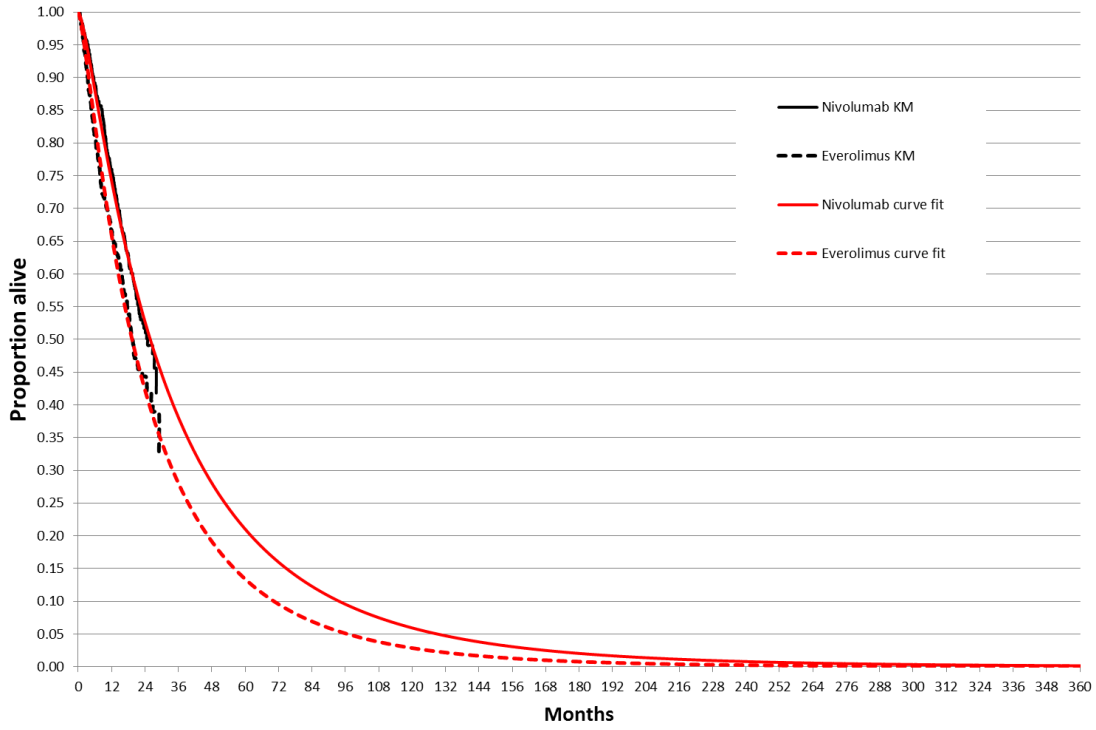
Figure 21. Base case OS curve fits to CheckMate 025 data (adapted from CS, pg 142, Figure 28)



Abbreviations in figure: KM, Kaplan Meier (curve).

The company reported that, "clinicians were surprised not to see a long-term relative survival benefit for nivolumab, in anticipation of an immune-response-based plateau similar to that observed in melanoma patients treated with nivolumab" (CS, pg 143, Section 5.3.1). The long-term projections of OS for nivolumab and everolimus, based on the selected generalised gamma model, are shown in Figure 22.

Figure 22. Base case OS curve fits to CheckMate 025 data (CS, pg 142, Figure 28)



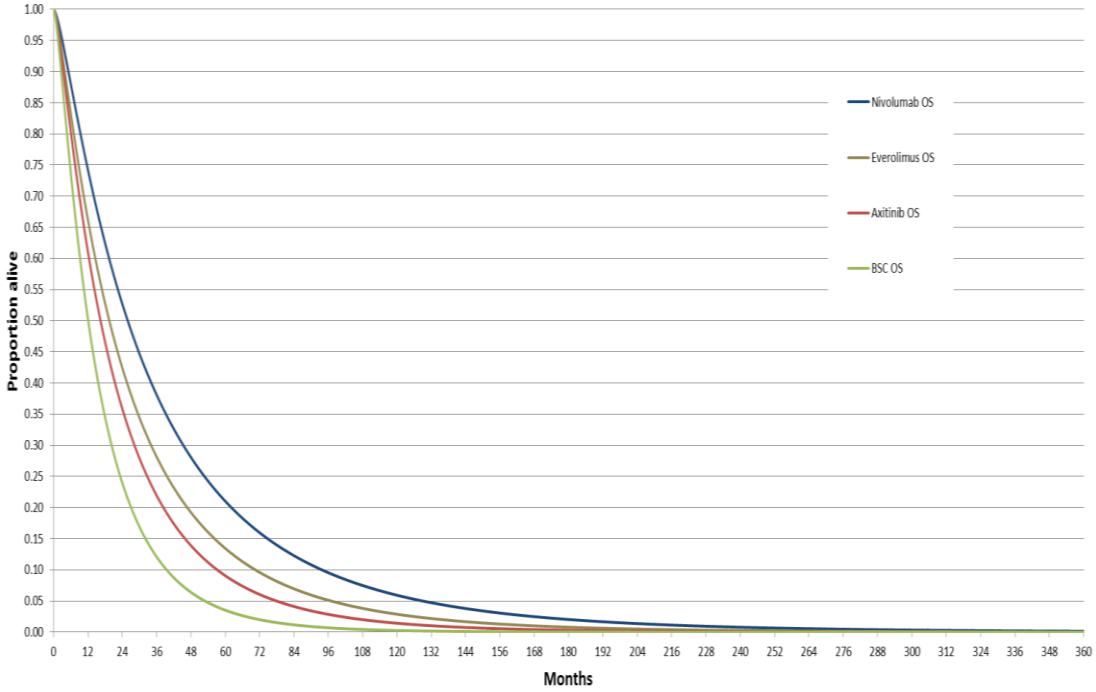
The OS for axitinib and BSC was determined by applying the HRs resulting from the NMA (Section 4.4.4) to the OS curve estimated for everolimus, under the assumption of equal effectiveness between BSC and placebo. In the base case model, the company applied the results of the crossover-adjusted analysis (detailed in Section 4.4.4). The HRs estimated for the comparison between everolimus and axitinib, and everolimus and placebo, are reported in Table 29. The ERG also reports the HR for the comparison against nivolumab for a comparison of the effect sizes.

Table 29. Crossover-adjusted hazard ratios estimated in the company's network meta-analysis

HR: everolimus vs	Crossover-adjusted HR	95% CI
Axitinib	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Abbreviations in table: CI, confidence interval; HR, hazard ratio.		

The OS curves used in the base case, resulting from the application of the crossover-adjusted HRs to the everolimus survival generalised gamma curve, are shown in Figure 23 for all comparators included in the company's analysis.

Figure 23. Base case OS curves, all treatment options (CS, pg 144, Figure 29)



Abbreviations in figure: BSC, best supportive care; OS, overall survival.

As part of the sensitivity analyses, the company reported the OS curves for all comparators estimated using the results from the intention-to-treat (ITT) NMA. The company stated that, "The crossover-adjusted NMA results are the most appropriate for analysis […] However, at clinical review, oncologists did not anticipate a survival advantage of everolimus over axitinib" (CS, pg 144, Section 5.3.1). The company included the extrapolated survival using the alternative NMA estimates based on the ITT HRs, reported in Table 30.

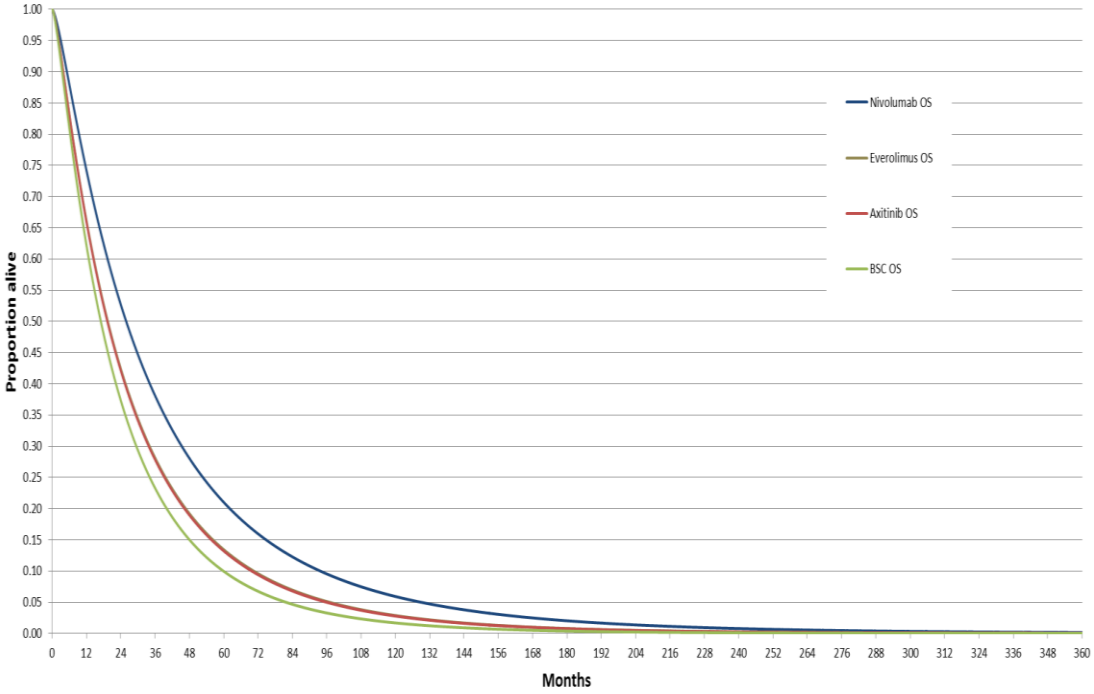
Table 30. Intention-to-treat hazard ratios estimated in the company's network meta-analysis

HR: everolimus vs	ITT HR	95% CI
Axitinib	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]

Abbreviations in table: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

The OS curves resulting from the scenario analysis are shown in Figure 24. The everolimus and axitinib curves are almost coincident, as the HR for the comparison between everolimus and axitinib was estimated equal to [redacted].

Figure 24. Scenario OS curves, using ITT NMA HRs (CS, pg 145, Figure 30)

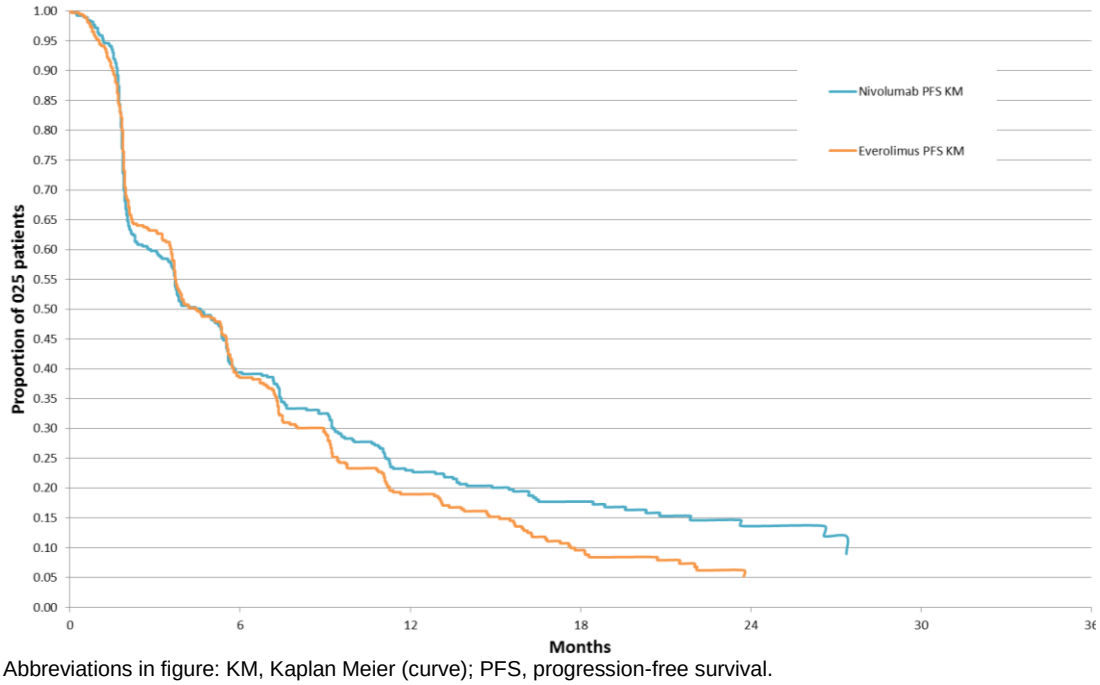


Abbreviations in figure: BSC, best supportive care; OS, overall survival.

5.4.2.2 Progression-free survival

The survival data observed in the CheckMate 025 trial for PFS are shown in Figure 25. The number of patients at risk over time is reported in Table 31.

Figure 25. KM PFS data, CheckMate 025 (CS, pg 146, Figure 31)



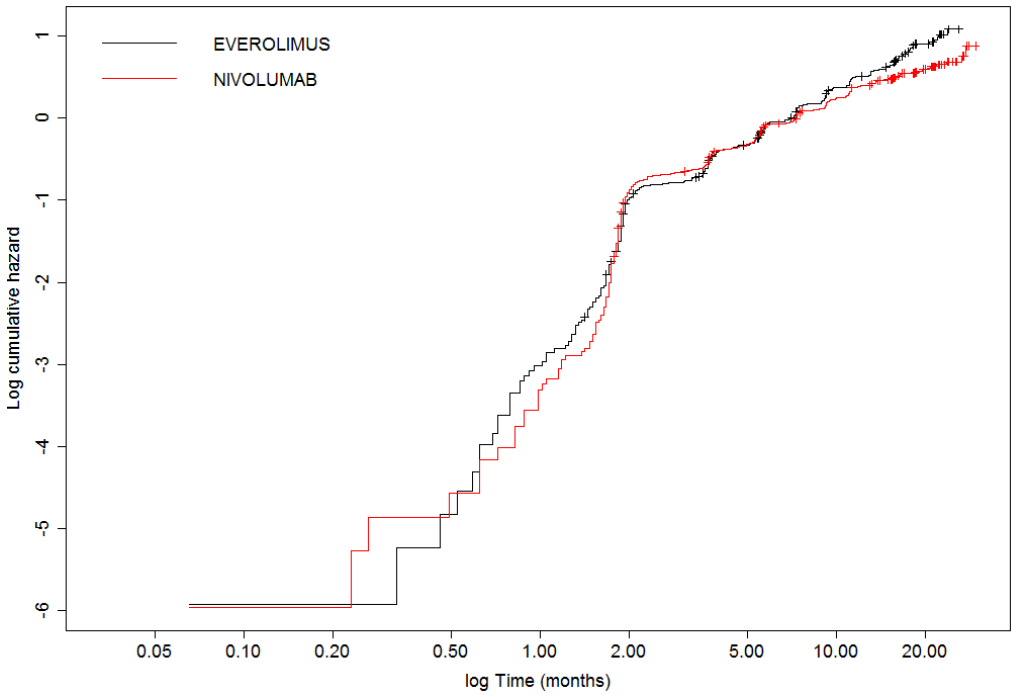
Abbreviations in figure: KM, Kaplan Meier (curve); PFS, progression-free survival.

Table 31. Number at risk over time, progression-free survival, CheckMate 025 (CS, pg 146, Table 32)

Months	0	3	6	9	12	15	18	21	24	27	30	33
NAR - Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
NAR - Everolimus	411	227	129	97	61	47	25	16	3	0	0	0
Abbreviations in table: NAR, number at risk.												

The company stated that, based on the analysis of the KM curves and the log-cumulative hazard plot shown in Figure 26, the PH assumption for the PFS data was not appropriate. No formal test or additional details were reported in support to this statement.

Figure 26. Log cumulative hazard plot, PFS in CheckMate 025 (CS, pg 147, Figure 32)



As the PH assumption was considered not to hold, parametric survival models were fit to the PFS trial data stratified by treatment arm, i.e. independently. Plots for the visual assessment of fit of the parametric models to the KM data are shown in Figure 27 and Figure 28 for the nivolumab and everolimus arms of the CheckMate 025 trial, respectively. The company noted that, "owing to the sharp initial fall in PFS, particularly in the first 3 months of the nivolumab treatment arm, and subsequent flattening of the curve in these patients after around 12 months, none of these models are sufficiently flexible to fit the PFS data accurately" (CS, pg 147, Section 5.3.2).

Figure 27. Parametric model fits to stratified PFS data from CheckMate 025, nivolumab arm (CS, pg 148, Figure 33)

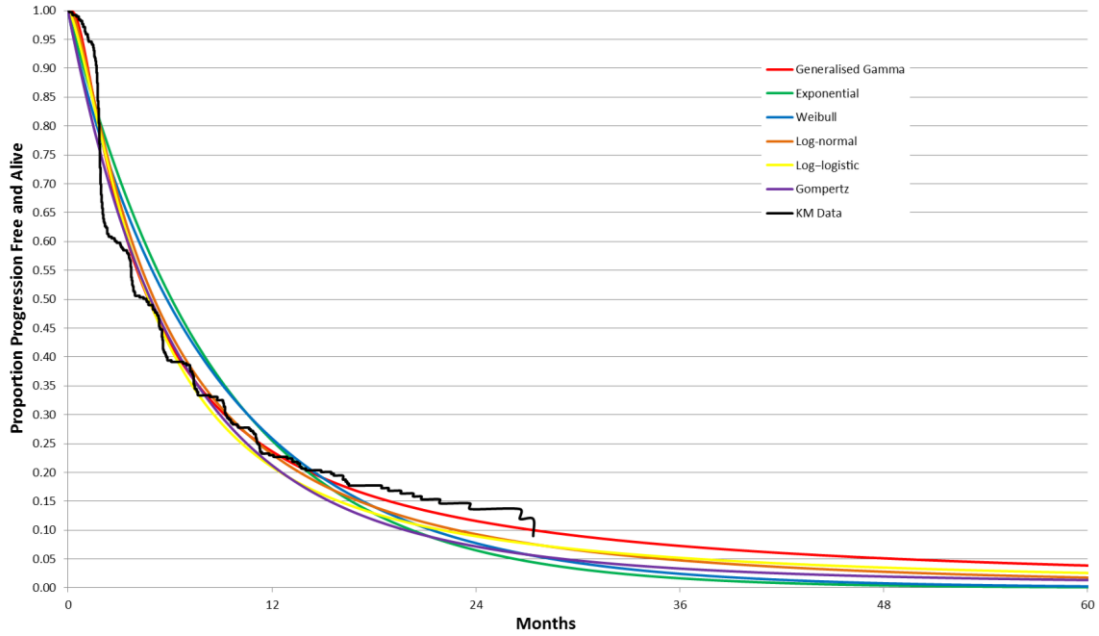
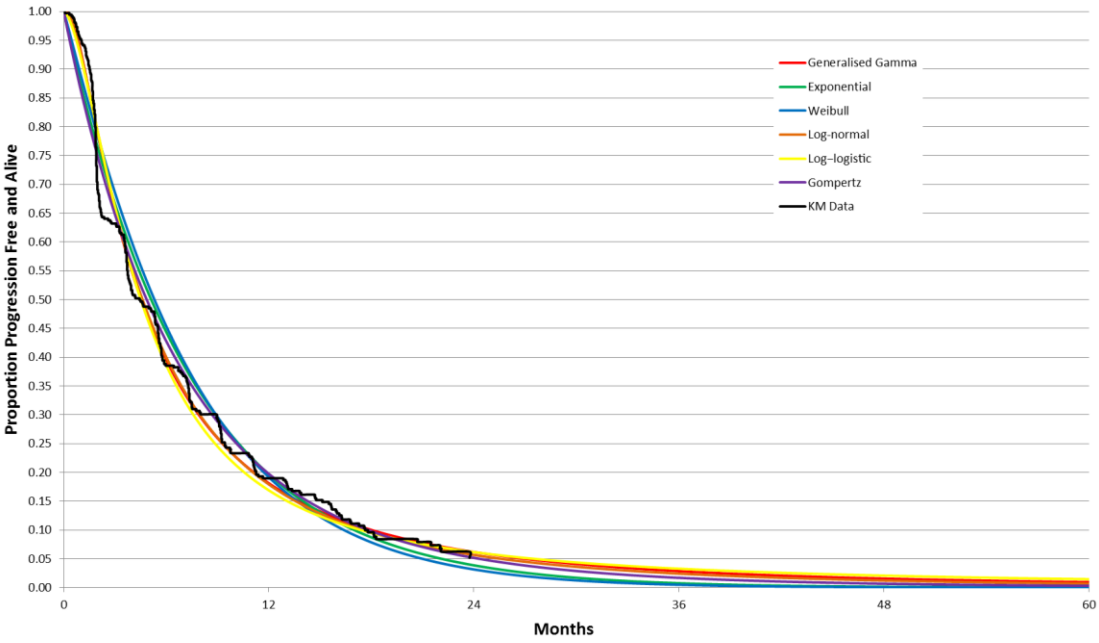


Figure 28. Parametric model fits to stratified PFS data from CheckMate 025, everolimus arm (CS, pg 148, Figure 34)



The company stated that the early steep drop in PFS might be related to the timing of the first scan for the assessment of progression, performed at 8 weeks from randomisation. The company hypothesised that, "the steep drop in the early weeks […] may represent a subgroup of patients with poorer prognosis […]; whereas the flat tail at the end may be representing those patients with better prognosis […]" (CS, pg 149, Section 5.3.2). This hypothesis granted the exploration of survival data using more flexible models. The company performed an analysis of the trial data using the spline-

based survival model of Royston and Parmar.[81] The number of internal knots was limited to a maximum of two, as the presence of more than 3 subgroups was considered clinically implausible. Three transformations of the survival function $S(t, \boldsymbol{z})$ were explored using natural cubic splines:

- The log-cumulative hazard, indicated by "hazard": $g\big(S(t, \boldsymbol{z})\big) = \log(-\log\big(S(t, \boldsymbol{z})\big)$;
- The log-cumulative odds, indicated by "odds": $g\big(S(t, \boldsymbol{z})\big) = \log(S(t, \boldsymbol{z})^{-1} - 1)$;
- The inverse normal cumulative distribution function, indicated by "normal": $g\big(S(t, \boldsymbol{z})\big) = \Phi^{-1}\big(S(t, \boldsymbol{z})\big)$.

The AIC and BIC statistics for all tested models are reported in Table 32 and Table 33, respectively for the nivolumab and everolimus arm.

Table 32. AIC and BIC statistics, model fits to stratified PFS data, nivolumab arm, CheckMate 025 (adapted from CS: pg 149, Table 33; pg 152, Table 35; response to clarification question C1, Table 8)

Model	AIC	BIC
Generalised gamma	1932.912	1944.961
Log-normal	1944.538	1952.570
Log-logistic	1951.954	1959.986
Gompertz	2006.797	2014.829
Weibull	2018.543	2026.575
Exponential	2020.251	2024.267
Spline models		
Spline 2 knot(s) – odds	1897.302	1913.367
Spline 2 knot(s) – hazard	1897.665	1913.730
Spline 1 knot(s) – odds	1909.947	1921.996
Spline 1 knot(s) – hazard	1915.430	1927.479
Spline 1 knot(s) – normal	1921.659	1933.708
Spline 2 knot(s) – normal	1923.369	1939.434

Abbreviations in table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.
Note: The BIC statistics for the spline models are reported from Table 8 of the response to clarification question C1.

Table 33 AIC and BIC statistics, model fits to stratified PFS data, everolimus arm, CheckMate 025 (adapted CS: pg 149, Table 34; pg 153, Table 36; response to clarification question C1, Table 9)

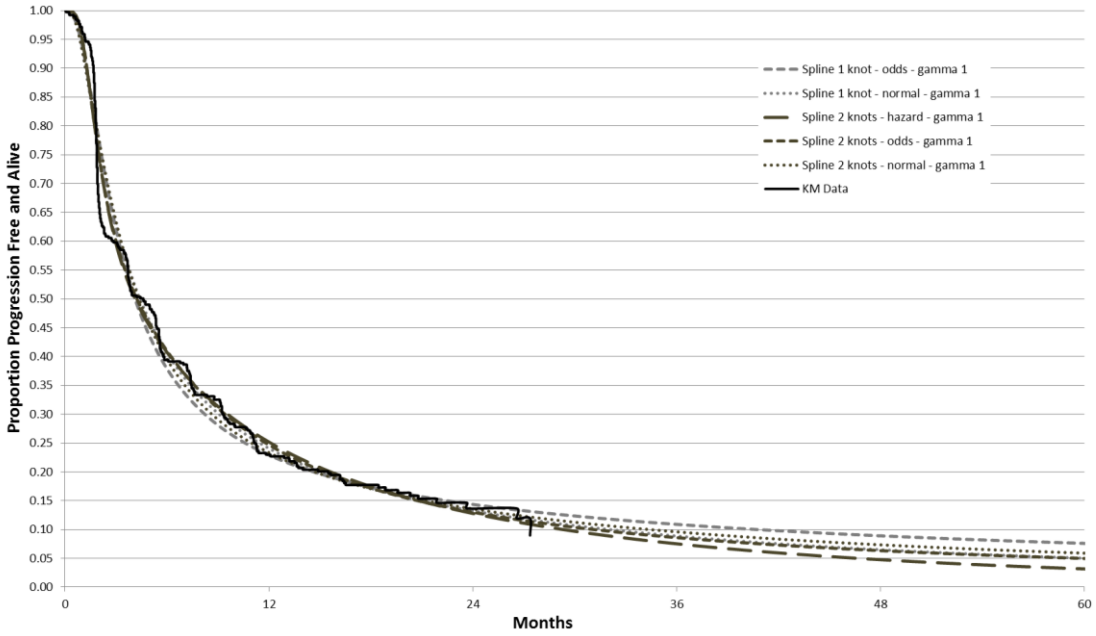
Model	AIC	BIC
Log-normal	1887.522	1895.559
Generalised gamma	1888.860	1900.916
Log-logistic	1896.486	1904.523
Gompertz	1933.468	1941.505
Weibull	1933.491	1941.529
Exponential	1933.562	1937.581
Spline models		
Spline 2 knot(s) – odds	1874.493	1890.568
Spline 2 knot(s) – hazard	1873.657	1889.731

Model	AIC	BIC
Spline 1 knot(s) – odds	1890.604	1902.660
Spline 1 knot(s) – hazard	1887.032	1899.088
Spline 1 knot(s) – normal	1887.476	1899.531
Spline 2 knot(s) – normal	1889.282	1905.357

Abbreviations in table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.
Note: the AIC statistics for the spline models are reported from Table 9 of the response to clarification question C1.

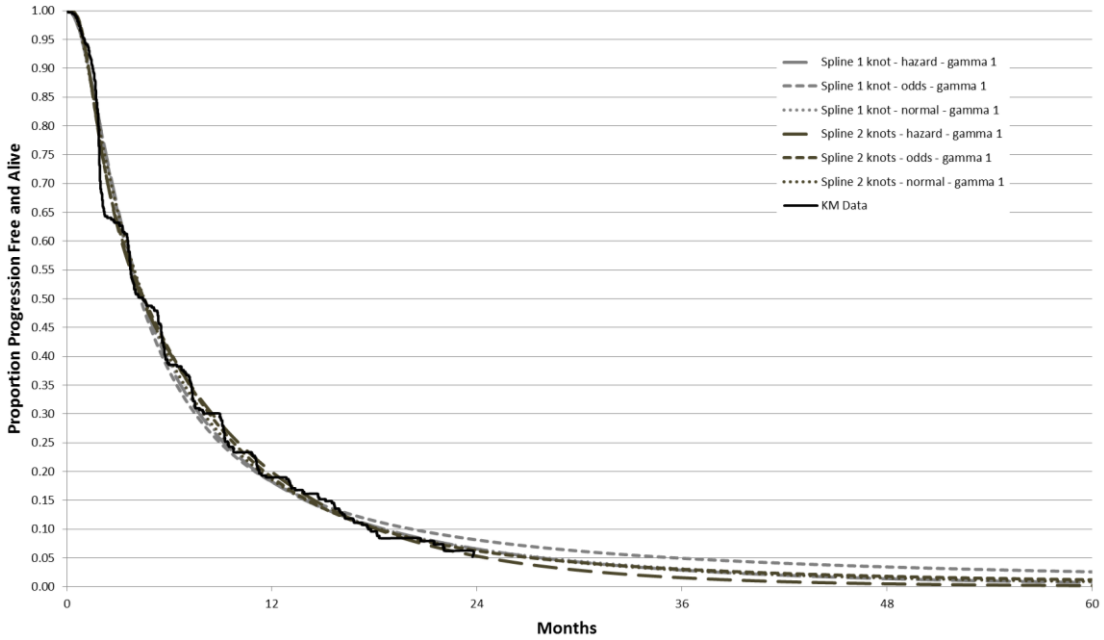
Figure 29 and Figure 30 show the spline model fits to the nivolumab and everolimus arms of the CheckMate 025 trial data, respectively. The company reported that, "Visual inspection and goodness-of-fit statistics [highlighted] the better accuracy of fit to the KM data than standard models, particularly for the nivolumab data" (CS, pg 151, Section 5.3.2). As the 2-knot "odds" spline models resulted in the lowest AIC and BIC measures, these were used to model PFS for both model arms in the company's base case analysis.

Figure 29. Spline model fits to stratified PFS data from CheckMate 025, nivolumab arm (CS, pg 151, Figure 35)



Abbreviations in figure: KM, Kaplan Meier (curve).

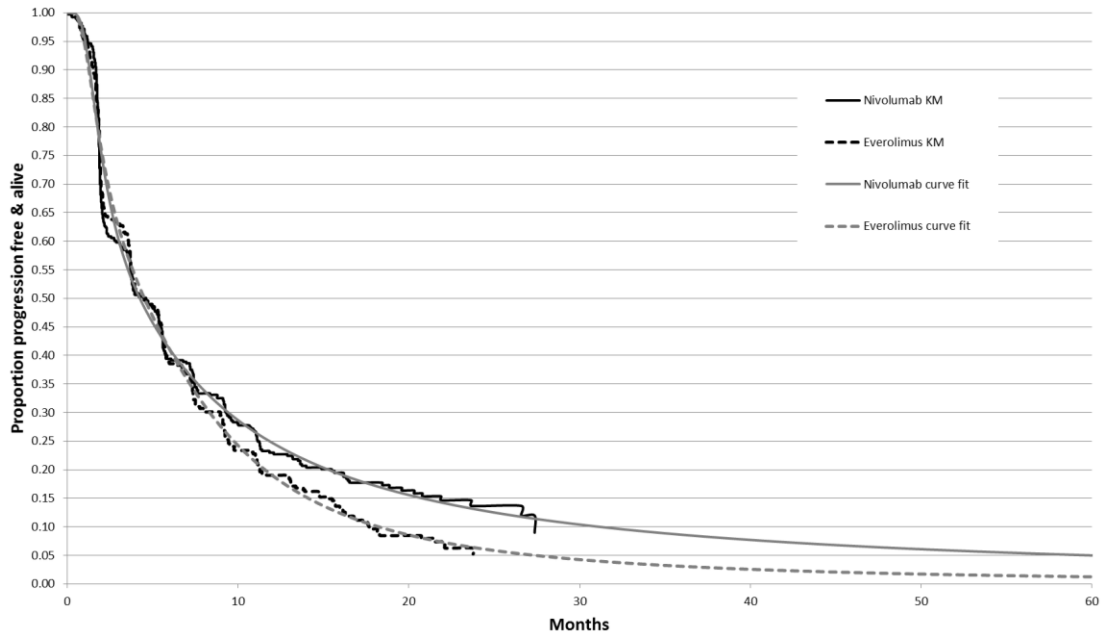
Figure 30. Spline model fits to stratified PFS data from CheckMate 025, everolimus arm (CS, pg 152, Figure 36)



Abbreviations in table: KM, Kaplan Meier (curve).

The PFS curves for nivolumab and everolimus, extrapolated using the 2-knot "odds" spline models as in the company's model, are shown in Figure 31.

Figure 31. Base case PFS curve fits to CheckMate 025 data (CS, pg 153, Figure 37)



Abbreviations in figure: KM, Kaplan Meier (curve).

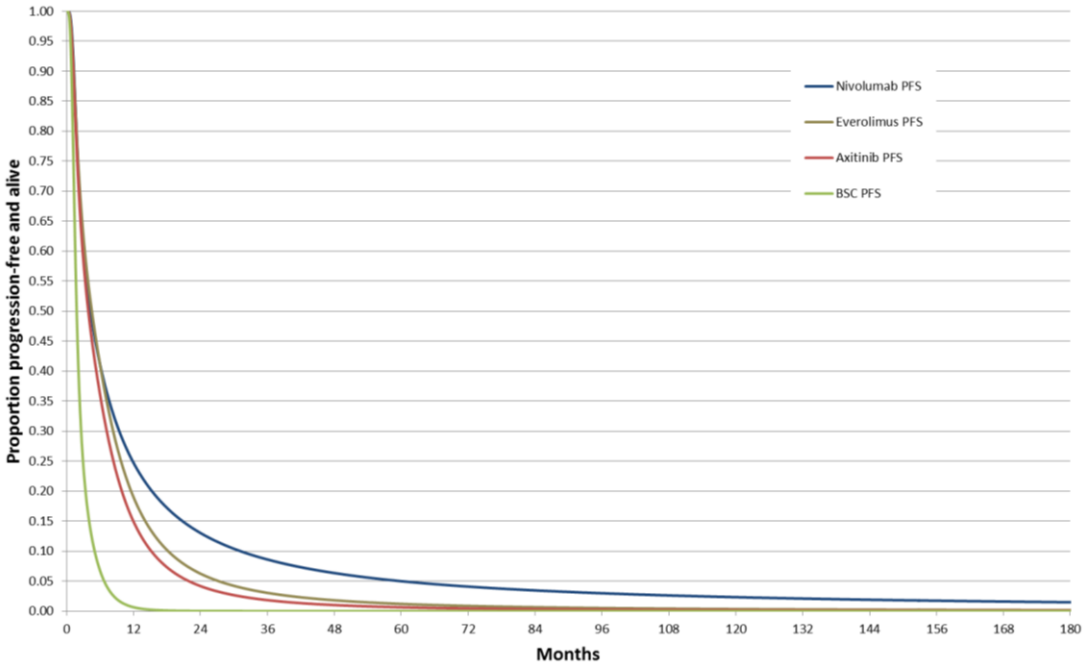
The PFS for axitinib and BSC was estimated by applying the HR estimated in the NMA to the everolimus curve, assuming that BSC was equally as effective as placebo. The HRs resulting from the company's NMA are reported in Table 34.

Table 34. Hazard ratios estimated in the company's network meta-analysis for progression-free survival

HR: everolimus vs	HR	95% CI
Axitinib	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Abbreviations in table: CI, confidence interval; HR, hazard ratio.		

Figure 32 shows the PFS curves for all four treatment options included in the model. Independent two-knot natural cubic spline models for the log-cumulative odds were used for nivolumab and everolimus; the BSC and axitinib curves were obtained applying the HRs in Table 34 to the everolimus curve.

Figure 32. Base case PFS curves, all treatment options (CS, pg 154, Figure 38)



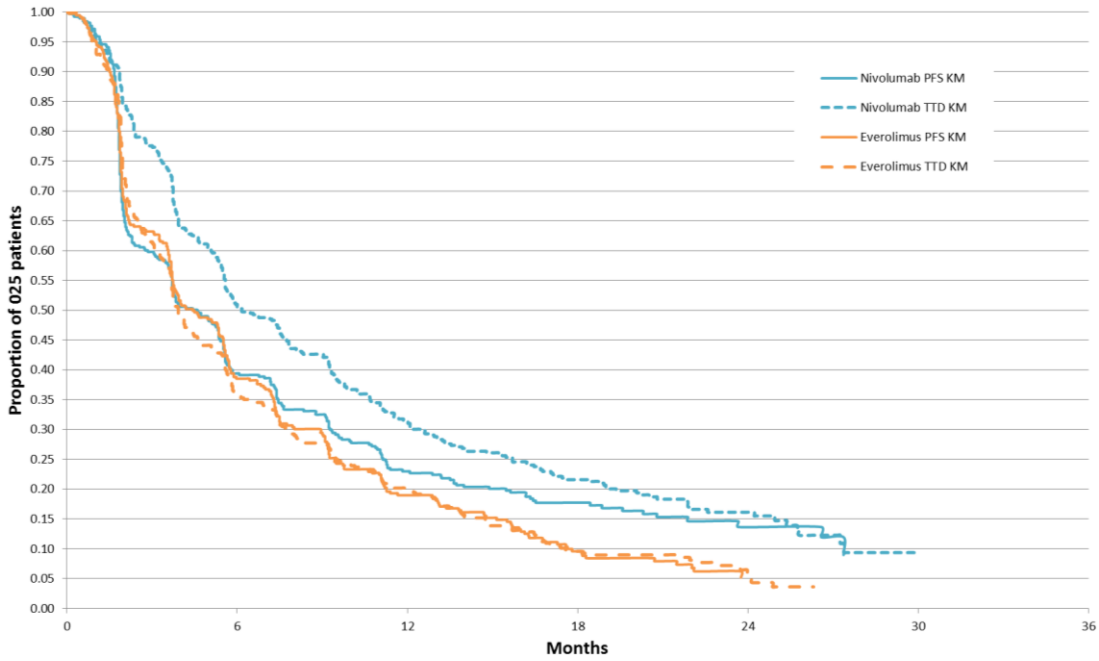
Abbreviations in figure: BSC, best supportive care; PFS, progression-free survival.

5.4.2.3 Time to discontinuation

The company modelled time-to-discontinuation (TTD) data into the model separately from PFS. This was because according to the posology of everolimus and axitinib, treatment with any of the drugs, "should continue as long as clinical benefit is observed or until unacceptable toxicity occurs"[82, 83]; for nivolumab, according to the draft Summary of Product Characteristics (SPC) provided by the company, "Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient" (Appendix 1 of CS, pg 5, Section 4.2). As discontinuation was not related directly (or explicitly) to disease progression for any of the drugs, it was modelled independent from PFS. TTD was used to partition alive patients by on- or off-treatment status in the model, to capture treatment acquisition and administration costs accurately. The survival data observed in the

CheckMate 025 trial are reported in Figure 33. The curves highlight that, while the TTD and PFS curves were very close together for everolimus, for nivolumab they diverged in the first 3 months, to converge again at about 2 years.

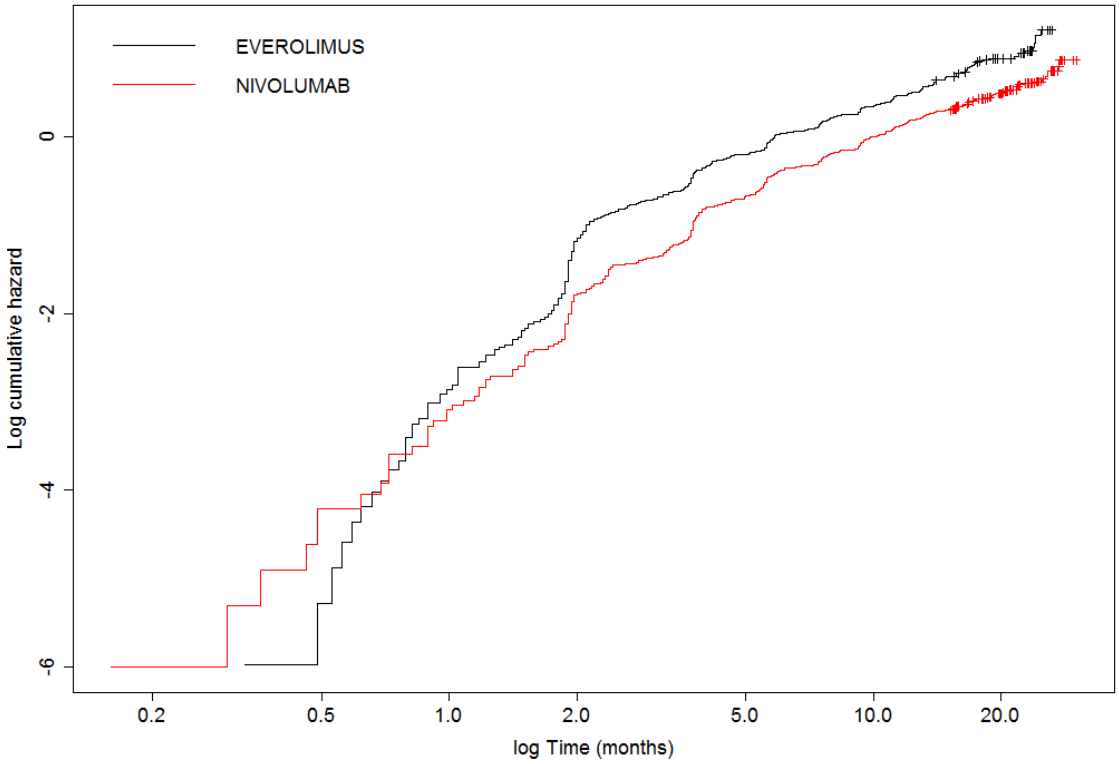
Figure 33. KM PFS and TTD data, CheckMate 025 (CS, pg 155, Figure 39)



Abbreviations in figure: KM, Kaplan Meier (curve); PFS, progression-free survival; TTD, time to (treatment) discontinuation.

The company used the same survival analysis approach to model TTD data as for PFS. The company reported to have assessed the appropriateness of the PH assumption graphically: from the analysis of the KM curves (Figure 33) and the log-cumulative hazard plot (Figure 34), "after initial separation, proportional hazards appears to hold across treatment arms of CheckMate 025. As such, single survival models were fit to the TTD dataset, un-stratified by treatment arm" (CS, pg 154-155, Section 5.3.3). No formal testing of the PH assumption was reported.

Figure 34. Log-cumulative hazard plot, time to discontinuation in CheckMate 025 (CS, pg 156, Figure 40)



The company tested standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma) as well as the spline-based survival models for their goodness of fit, analogously to the analysis performed on PFS data (detailed in Section 5.4.2.2). The justification for using spline models is reported in Box 5.

Box 5. Company's justification to the use of spline-based models for the anlaysis of TTD data (CS, pg 156, Section 5.3.3)

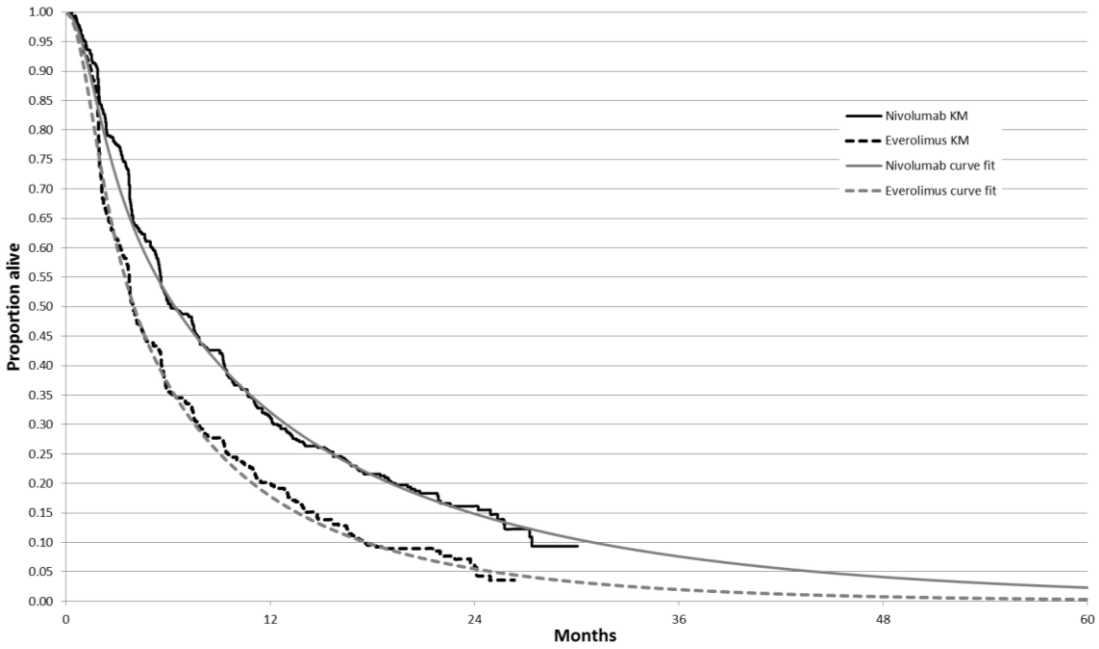
However, on the everolimus arm, even the best fitting standard models struggle to fit the steep early curve and subsequent flattening also seen in the PFS data. Parametric cubic spline models were again explored as a more flexible alternative. […] These models provide a better visual fit to the TTD data.
Abbreviations in box: PFS, progression-free survival; TTD, time to (treatment) discontinuation.

The company stated that the comparison between the AIC and BIC statistics of the standard parametric models and spline-based models, "illustrates that the better-fitting of these models also provide a better statistical fit than the best-fitting standard parametric models" (CS, pg 156, Section 5.3.3). The two-knot spline "hazard" model was chosen as the base case model because it was associated with the lowest AIC among the tested functions. Figure 35 shows the fit of the selected model (2-knot "hazard" spline) fitted to the CheckMate 025 TTD data.

Table 35. AIC and BIC statistics, model fits to unstratified TTD data, CheckMate 025 data (adapted from CS, pg 158-159, Table 37 and Table 38)

Model	AIC	BIC
Generalised gamma	4429.807	4448.561
Log-normal	4432.481	4446.546
Log-logistic	4449.747	4463.812
Gompertz	4525.747	4539.812
Exponential	4532.696	4542.073
Weibull	4533.875	4547.940
Spline models		
Spline 2 knot(s) – hazard	4415.016	4438.458
Spline 2 knot(s) – odds	4418.138	4441.580
Spline 1 knot(s) – normal	4424.155	4442.909
Spline 2 knot(s) – normal	4425.559	4449.001
Spline 1 knot(s) – hazard	4425.759	4444.513
Spline 1 knot(s) – odds	4429.522	4448.275
Abbreviations in table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

Figure 35. Base case TTD curve fits to CheckMate 025 data (CS, pg 160, Figure 45)



Abbreviations in figure: KM, Kaplan Meier (curve).

In the absence of TTD data for axitinib, the company assumed that treatment was continued until disease progression. As no treatment duration was associated to BSC, no assumptions on TTD were necessary.

5.4.3 Adverse events

The company included the following Serious Grade III and IV treatment-related adverse events (TRAEs) in the model: pneumonitis, diarrhoea, anaemia, and pneumonia. The rates and durations of TRAEs for patients receiving nivolumab and everolimus in the model were based on their incidence

in the CheckMate 025 trial.[39] The incidence and median durations of serious TRAEs are reported in Table 36.

Table 36. Incidence and duration of Serious Grade III/IV treatment emergent adverse events (adapted from CS, pg 170, Table 45)

Event	Nivolumab		Everolimus	
	Proportion of patients experiencing the event	Median duration (weeks)	Proportion of patients experiencing the event	Median duration (weeks)
Pneumonitis	1.5%	2.71	1.9%	3.14
Diarrhoea	1.0%	3.21	0.2%	3.00
Anaemia	0.5%	4.21	1.2%	4.21
Pneumonia	0.0%	0.71	1.0%	0.71
Company's note: [a] Everolimus data were unavailable, assumed to be equal to nivolumab. Source: CheckMate 025 Duration of event data[39]				

The company assumed that the impact of TRAEs on HRQoL was captured within the EQ-5D data collected in the CheckMate 025 and AXIS trials, therefore this was not explicitly modelled in the base case analysis.[79] The company justified this assumption stating that, "patient-level EQ-5D data are used to capture HRQL across all model arms in the base case analysis, and the HRQL effects of treatment-emergent AEs are expected to be captured by these data" (CS, Section 5.4.3, pg 168).

Resource use for management of TRAEs was accounted for in the model and based on the incidence rates reported in the CheckMate 025 trial.[39]

5.4.4 Health-related quality of life

In this Section, the ERG reports the sources of HRQoL data used in the cost-effectiveness analysis, and how it was translated into quality-adjusted life years (QALYs) in the model, as reported in Section 5.4 of the CS.

The company stated not to have sufficient time to carry out a systematic literature search for sources of HRQoL data for this submission. However, the company reviewed the search carried out in the single technology appraisal: axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (TA 333), and the analysis done in the AXIS trial as reported in Section 5.4.2 of the CS.[78, 79]

Health state utility values (HSUV) for patients receiving nivolumab and everolimus were based on the statistical analysis of EQ-5D data collected in the CheckMate 025 trial as described in Box 6. Completion rates of EQ-5D questionnaires at each visit were provided by the company in Section

5.4.1 of the CS. The company reported that UK EQ-5D tariffs were used for valuation of patient responses.

Box 6. Description of EQ-5D data collection in CheckMate 025 (CS, pg 160-161, Section 5.4.1)

The EQ 5D questionnaire was completed in CheckMate 025; before any clinical activities, after randomisation, on Day 1 of each 4-week cycle, and at the first two follow-up visits (approximately 30 days and approximately 100-114 days after last dose). Assessments were performed prior to any study-related procedures. Compliance rates for EQ-5D completion were good across time-points […]. The UK EQ-5D tariff was used to value patient questionnaire responses.
Abbreviations in box: EQ-5D, EuroQol-five dimension

A linear mixed model was fit to the EQ-5D data, with fixed covariates for the effects of progression status, treatment allocation, and the interaction between treatment arm and progression status, and with a random effect for subject. This model was selected to account for within-patient correlation and to assess the difference in patients' HRQoL according to progression status and treatment received. The results of the model are presented in Table 37. The company's model revealed a 0.036 decrement in utility associated with being assigned to everolimus rather than nivolumab and a 0.069 decrement upon disease progression. The company proposed a possible explanation for the decrement associated with the allocation to the everolimus arm, presented in Box 7.

Table 37. Statistical model results using EQ-5D data from CheckMate 025 (CS, pg 166, Table 40)

Parameter	Estimate	Standard error	P value
Constant	0.798	0.010	<.0001
Decrement assigned to comparator arm	-0.036	0.015	0.017
Decrement for disease progression	-0.069	0.007	<.0001
Decrement for interaction between disease progression and assigned to comparator arm	0.005	0.010	0.654

Box 7.Possible explanations for utility decrement associated with everolimus (CS, pg 165, Section 5.4.1)

The smaller, but significant, negative effect of randomisation to everolimus upon utility may be explained by lower response rates in the everolimus arm as compared with nivolumab. In addition, it is a reasonable assumption that knowledge of responding to study drug is likely to impact patient utility […] for pre-progressive patients. For post-progressive patients, clinicians reported that higher utility is expected for nivolumab patients, due to both (i) treatment continuing beyond progression in many cases, and (ii) the immune-response mechanism of nivolumab that implies benefit beyond RECIST-defined progression and beyond treatment discontinuation.
Abbreviations in box: RECIST, Response Evaluation Criteria in Solid Tumors.

In the absence of HSUVs from a head-to-head trial including axitinib and BSC, values used in the TA 333 were used for the base case analysis to estimate QALYs in the company's analysis. The HSUVs PFS and PPS used in TA 333 were derived from mean on-treatment utility and mean utility at treatment discontinuation estimates collected in the AXIS trial. It was assumed in TA 333 that HSUVs for axitinib and BSC were equal, with the justification that disease symptoms while on BSC were comparable to the toxicity experienced by patients receiving axitinib.[78] The same assumption, i.e. equal HSUVs between axitinib and BSC, was made by the company for the current submission. The HSUVs used in the model for all the comparators are reported in Table 38. The utility values estimated for PFS for nivolumab, everolimus, axitinib and BSC were 0.80, 0.76, 0.69 and 0.69, respectively. The corresponding estimates for PPS were 0.73, 0.70, 0.61 and 0.61 for nivolumab, everolimus, axitinib and BSC, respectively. These estimates suggest that even after progressing, patients on nivolumab and everolimus would enjoy a superior HRQoL than patients who have not yet progressed when receiving axitinib or BSC.

Table 38. Health state utility values used in cost-effectiveness analysis (adapted from CS, Table 49, pg 172)

Health State	Utility value	Source
PFS		
Nivolumab	0.80	CheckMate 025
Everolimus	0.76	CheckMate 025
Axitinib	0.69	TA 333[78]
BSC	0.69	Assumption
PPS		
Nivolumab	0.73	CheckMate 025
Everolimus	0.70	CheckMate 025
Axitinib	0.61	TA 333[84]
BSC	0.61	Assumption
Abbreviations in table: BSC, best supportive care; PFS, progression-free survival, PPS, post-progression survival.		

The company assumed that the effect of TRAEs on HRQoL was already incorporated within the HSUVs in the base case analysis, as patient-level EQ-5D data were used to inform the values for all the comparators. This assumption was tested as part of the scenario analyses carried out by the company.

5.4.5 Resources and costs

In this Section, the ERG summarises the estimates of resource use and costs included in the model. The company stated that there was not sufficient time to carry out a systematic review to identify evidence on resource use and costs for the management of advanced RCC. Costs were included in the

model from an NHS and PSS perspective, with the exception of terminal care costs which were partly funded by the voluntary sector. This is discussed further in Section 5.5.8.

The resource use and costs considered in the model were:

- Intervention and comparator costs, described in Section 5.4.5.1;
- Health state resource use and costs, described in Section 5.4.5.2;
- Adverse events costs described in Section 5.4.5.3;
- Subsequent therapy costs described in Section 5.4.5.4.

5.4.5.1 Intervention and comparator costs

The intervention and comparator costs in the model consisted of drug acquisition and administration costs. The acquisition costs for the intervention and comparator drugs are summarised in Table 39.

Table 39. Unit costs for drugs (adapted from CS, pg 175, Table 50)

Drug	Formulation (mg)	Vials/tabs per pack	Price per vial/pack	Source for price
Nivolumab	40	1	£439.00	Bristol Myers Squibb
	100	1	£1,097.00	
Everolimus	10	30	£2,673.00	MIMS[a(85)]
Axitinib	5	56	£3,517.00	MIMS[b(85)]

Abbreviations in table: mg, milligram; tabs, tablets.
Notes: [a](Antineoplastics - Afinitor) Accessed 20 January 2016; [b] (Antineoplastics - Inylta) Accessed 20 January 2016

In the CheckMate 025 trial, patients received less than the planned nivolumab or everolimus doses. The company assumed that patients in the model would not receive the planned dose quantity of nivolumab or everolimus, but that the quantity would be reduced as observed in the CheckMate 025 trial. The total axitinib quantity received was similarly based on the ratio between the dose received and the dose planned in the AXIS trial, reported in TA 333[(78)]. The proportions of the planned doses assumed to be received by patients were calculated by the company as reported in Box 8, and are presented in Table 40.

Box 8. Calculation of planned doses received for comparators (CS, Section 5.5.2, pg 174)

The proportion of planned nivolumab doses received was calculated from CheckMate 025 patient-level data as 92.425%, accounting for the proportion of doses delayed (5.075%; average dose delay was 14 days), and the proportion of doses omitted (2.5%). To calculate the proportion of planned everolimus doses received from patient-level data, the sum product of number of packs required to cover sum days of tablets received and maximum number of 28-day treatment pack cycles on

treatment was calculated, as 94.240%. To account for the relative dose intensity observed for axitinib in the AXIS study and for consistency with TA333, as described in […], the proportion of 5mg twice daily axitinib doses received by axitinib patients is assumed to be 102.0%.

The mean weight of patients in the Western Europe population in CheckMate 025 was used to inform the weight of patients in the model. The method of moments was used to estimate the number of vials used by patients receiving nivolumab, under the assumption that the weight was distributed log-normally. Drug wastage for nivolumab was assumed in the base case analysis, allowing no vial sharing.

Table 40. Dosage and weekly drug costs (adapted from CS, pg 175, Table 50)

Drug	Planned dosing regimen	Formulation (mg)	Vials/ tabs per admin	Proportion of dose received	Cost per weekly cycle
Nivolumab	3mg/kg, every 2 weeks IV	40	1.73	92%	£878.96
		100	1.99		£402.79
Everolimus	10 mg, one tablet per day	10	1.00	94%	£587.77
Axitinib	5 mg, one tablet twice a day	5	1.00	102%	£896.84
Abbreviations in table: IV, intravenous; kg, kilogram; mg, milligram.					

Drug administration costs were included only for nivolumab, assumed to be administered in an outpatient setting, as the comparator drugs (i.e. everolimus and axitinib) are administered orally. The cost of nivolumab administration, presented in Table 41, was applied weekly in the model. The ERG notes that, according to the NHS Reference Costs, the correct value was £185.53, and not £186.53 as reported in the CS. [86] This resulted in a weekly administration cost of £92.77, in accordance to the bi-weekly schedule.

Table 41. Administration costs for nivolumab (CS, pg , Table)

Administration cost for nivolumab	Unit cost	Source
Administration of intravenous therapy	£185.53[a]	NHS Reference Costs 2014-2015 Outpatient, Simple parenteral chemotherapy, Currency code SB12Z[86]
Abbreviations in table: NHS, National Health Service. Note: [a]This value was reported incorrectly as £186.53 in the CS.		

5.4.5.2 Health state resource use and costs

Resource use for the management of pre- and post-progression advanced RCC was estimated and included in the model as presented in Table 42. Disease management before progression was assumed to involve general practitioner (GP) visits, computerised tomography (CT) scans and blood tests.

Progressed patients were assumed to receive care in the form of GP and community nurse visits, in addition to pain medications.

Table 42. Resource use for management of advanced RCC (CS, pg 177, Table 52)

Resource	Frequency per week	Frequency source	Cost	Cost source
PFS				
GP visit	0.25	TA 333	£37.00	PSSRU (2015) Section 10.8 p177, General practitioner - unit costs, Patient contact lasting 11.7 minutes, including direct staff costs, excluding qualifications[87]
CT scan	0.08	TA 333	£136.21[a]	NHS reference costs 2014-15; "Diagnostic imagining, outpatient, CT scan more than 3 areas", RD27Z[86]
Blood test	0.25	TA 333	£3.01[b]	NHS reference costs 2014-15; "Directly assessed pathological services - haematology", DAPS05[86]
PPS				
GP visit[c]	0.25	TA 333	£37.00	PSSRU (2015) Section 10.8 p177, General practitioner - unit costs, Patient contact lasting 11.7 minutes, including direct staff costs, excluding qualifications[87]
Specialist community nurse visit	0.38	TA 333	£65.00	PSSRU (2015) Section 10.4 p172, Nurse specialist (community), 1 hour patient time, excluding qualifications[87]
Pain medication	7.00	TA 333	£5.30	TA333 (BNF section 4.7.2 Opioid analgesics (morphine sulphate 1 mg/mL, net price 5-mL vial = £5.00), adjusted to 2014/2015 prices using PSSRU (2015) Section 116.3 p242, The hospital & community health services (HCHS) index[78, 87]

Abbreviations in table: BNF, British National Formulary; CT, computerised tomography; GP, general practitioner; mL, millilitre; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; PFS, progression-free survival; PPS; post-progression survival; PSSRU, Personal Social Services Research Unit.

Notes: [a] This value was reported incorrectly as £136.00 in CS; [b] This value was reported incorrectly as 3.00 in CS; [c] The description of cost source was reported incorrectly in the CS.

The cost of terminal care (TC) was applied to patients in the eight weeks prior to death. It was assumed to consist of community care and acute care, as described in a report by the King's Fund on improving choice at the end of life.[88] The cost for eight weeks of care, inflated to 2014/2015 prices, was £6,159.66 therefore a cost of £769.96 per week was applied in the model to patients in the terminal care health state.

A scenario analysis was carried out that assumes that consultant visits (instead of GP visits) and blood tests take place during treatment at each occurrence of treatment administration. The results of the analysis are presented in Section 5.6.2.

5.4.5.3 Adverse event costs

The costs of management of Serious Grade III/IV treatment-related adverse events (TRAEs) observed in more than 1% of patients in either arm of the CheckMate 025 trial were included in the model. The company reported that, "a targeted search of the literature revealed scant data on resource use associated with AEs" (CS, Section 5.5.4, pg 178). The Serious Grade III/IV TRAEs included were pneumonitis, diarrhoea, anaemia and pneumonia, and the respective management costs were applied weekly in the model. The costs associated with the management of TRAE episodes and the weekly costs applied in the model are summarised in Table 43 and

Table 44, respectively.

Table 43. Cost per episode of treatment-related adverse events (CS, pg 179, Table 53)

Serious Grade III/IV TRAE	Cost per episode	Source
Pneumonitis	£418.91	Bronchoscopy (19 years and over): £316, regular day and night admissions (DZ69A) NHS reference costs 2014-2015[86]
		Weekly OP appointments with a GP: 11.7 minutes of patient contact, excluding direct staff costs and without qualifications £33. Average across both arms is 2.93 weeks = £96.53 per episode (PSSRU 2015)[87]
		Four weeks of steroids: Fluticasone propionate, 50 microgram per inhalation, 60 inhalations=£6.38 (based on 100mg (i.e. 2 inhalations) per day for 30 days) (MIMS, http://www.mims.co.uk/drugs/respiratory-system/asthma-copd/flixotide-evohaler)[85]
Diarrhoea	£35.83	GP appointment (from PSSRU 2015, excluding direct staff costs, without qualifications, per patient contact lasting 11.7 minutes) £34[87]
		Loperamide (dose for acute diarrhoea, 4mg initially, then 2mg after each loose stool; max 16mg daily, from MIMS, assuming the entire prescription is filled) 2mg cap, 30=£1.83
Anaemia	£421.62	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9[86]
Pneumonia	£640.60	Lobar, atypical or viral pneumonia without interventions with CC score 7-9 = £399 (DZ11T), Regular day and night admissions, NHS reference costs 2014-2015[86]
		Computerised tomography scan of one area, without contrast, 19 years and over (RD20A), £85, diagnostic imaging.[86]
		Ampicillin, 500mg powder for solution for injection in vial, 10=£78.30, assuming 500mg four times daily (four administrations per day for 5 days = 20 administrations) £156.60 (MIMS, http://www.mims.co.uk/drugs/infections-and-infestations/bacterial-infections/ampicillin)[85]
Abbreviations in table: CC, complication or comorbidity; GP, general practitioner; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OP, outpatient; PSSRU, Personal Social Services Research Unit; TRAE, treatment-emergent adverse event.		

Table 44. Weekly costs for management of treatment-emergent adverse events (CS, pg 180, Table 54)

Serious Grade III/IV AE	Event costs	Nivolumab	Everolimus
		Cycle probability	Cycle probability
Pneumonitis	£418.91	0.001	0.001
Diarrhoea	£35.83	0.000	0.000
Anaemia	£421.62	0.000	0.001
Pneumonia	£640.60	0.000	0.001
Total AE cycle cost	**-**	**£0.35**	**£1.31**
Abbreviations in table: AE, adverse event.			

5.4.5.4 Subsequent therapy costs

The company justified including subsequent therapies (i.e. beyond second line) in the model by stating that patients in the CheckMate 025 trial could go on to receive further treatment. The company included all the subsequent therapies administered to more than 5% of patients in the trial, with the exception for bevacizumab given that it is not a treatment option within NHS England. The proportions of patients receiving the subsequent therapies, reweighted after excluding bevacizumab, are presented in Table 45.

Table 45. Proportion of patients receiving subsequent therapies in CheckMate 025, reweighted without bevacizumab (CS, pg 182, Table 56)

Subsequent treatment	From	
To	Nivolumab	Everolimus
Axitinib	25.21%	38.84%
Everolimus	26.74%	6.00%
Pazopanib	9.42%	16.68%
Sorafenib	6.62%	9.91%
Sunitinib	7.13%	8.86%
Total	**75.12%**	**80.29%**
Note: Totals do not sum to 100%; not all patients progressed to further therapy		

The same unit costs and dosage for everolimus reported in Table 39 and Table 40 were applied to calculate its costs as a subsequent therapy. The unit costs and dosages for sorafenib, sunitinib and pazopanib are reported in Table 46. An average treatment duration of 3.65 months (15.87 weeks) was assumed for all subsequent therapies, based on data from the GOLD trial, which compared dovitinib and sorafenib as third line therapy options in patients with RCC.[37]

The total cost for subsequent therapies for patients discontinuing treatment with axitinib was assumed to be the same as for patients discontinuing treatment with everolimus. Patients receiving BSC were assumed not to receive any subsequent therapy. The cost of subsequent therapy was applied as a one-off cost upon treatment discontinuation in the model. A summary of the total costs associated with subsequent therapies in the model for each intervention are summarised in Table 47.

Table 46. Dosage and costs of sorafenib, sunitinib and pazobanib (CS, pg 183, Table 57)

Drug	Formulation (mg)	Cost per vial/pack	Vials/tabs per admin	Vials/tabs per pack	Dose	Unit	Treatments per week	Method	Proportions of doses received	Total cost per week	Source
Sorafenib	200	£2,980.47	2.00	112	400	mg	14	Oral	100%	**£745.00**	MIMS [a(85)]
Sunitinib	50	£3,138.80	1.00	28	50	mg	4.7	Oral	100%	**£526.87**	MIMS [b(85)]
Pazopanib	400	£1,121.00	2.00	30	800	mg	14	Oral	100%	**£1,046.27**	MIMS [c(85)]

Abbreviations in table: admin, administration; mg, milligrams; MIMS, Monthly Index of Medical Specialties; tabs, tablets;

Notes: [a] (Antineoplastics - Nexavar) Accessed 20 January 2016, reported as £2980.00 in CS; [b] (Antineoplastics - Sutent) Accessed 20 January 2016; [c] (Antineoplastics - Votrient) Accessed 20 January 2016.

Table 47. Subsequent therapy costs across model arms (CS, pg 184, Table 58)

Intervention / Comparator	One-off subsequent treatment cost
Nivolumab	£9,026.29
Everolimus	£10,770.91
Axitinib	£10,770.91
BSC	£0.00

Abbreviations in table: BSC, best supportive care.

5.4.6 Discounting

The company applied an annual discount rate of 3.5% for costs and health effects in the model for the base case analysis, in line with the NICE reference case.[80] Discounting was applied weekly in the model.

Alternative discount rates of 0% and 6% were used in scenario analyses as reported in Section 5.6.2.

5.4.7 Sensitivity analysis

The company carried out a series of sensitivity analyses to test the robustness of the results to changes in assumptions and parameter values. The analyses were both deterministic (one-way parameter variations and scenario analyses) and probabilistic (PSA). The list of the sensitivity analyses performed and the results are reported in Section 5.6.2.

5.4.8 Model validation

In Section 5.10.1 of the CS it is reported that several assumptions and model inputs were validated by oncologists, and that the model was reviewed by an economist not involved in its adaptation. Details of model validation reported in the CS are presented in Box 9.

Box 9. Validation of model (CS, Section 5.10.1, pg 210)

Meetings with oncologists, each currently treating patients with advanced RCC within the NHS in England or Wales and each with some experience of HTA, were a crucial step in validating and informing key analysis assumptions. […] Each meeting comprised a 60-90 minute discussion, covering five pre-defined topics: the suitability of the proposed model to capture key outcomes; validation of survival extrapolations; the patient HRQL experience and validity of utility estimates; validation of resource use estimates from TA333; resources and patient HRQL associated with key adverse events. Notes from each of those meetings are disclosed as part of this submission. The model was quality-assured by the internal processes of the external economists who adapted the economic model. In these processes, an economist not involved in model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions
Abbreviations in box: HRQL, health-related quality of life; HTA, health technology assessment; NHS, National Health Service; RCC, renal cell carcinoma.

The company also reports (in Section 5.3.2 of the CS) to have consulted with clinical experts and external health economists regarding the appropriateness of the extrapolations based on parametric survival models and the suitability of using spline based survival models for the analysis of data observed in the CheckMate 025 trial.

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 48 and Table 49 summarise the ERG's quality assessment of the company's economic evaluation. Table 48 summarises the ERG's appraisal of the economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.[23] Table 49 reports the ERG's appraisal of the company's *de novo* economic models using the Philips checklist.[89]

Table 48. NICE reference case checklist for the base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes.
Perspective costs	NHS and Personal Social Services	Yes. A proportion of the costs in the terminal care health state is reported to be paid by the voluntary sector, but this was shown not to influence the model results.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	No. The company states that there was insufficient time to carry out systematic reviews. The ERG considers this reasonable, as the single technology appraisal (STA) was originally part of a multiple technology appraisal (MTA), and the change did not allow sufficient time for the company to perform a full systematic review.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Not reported clearly. The company stated that, "The UK EQ-5D tariff was used to value patient questionnaire responses" (CS, pg 161, Section 5.4.1) but did not include references or additional details.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	EQ-5D questionnaires administrated to patients in the CheckMate 025 trial. The sample was not representative of the public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations used in the table: EQ-5D, EuroQol-five dimensions questionnaire; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal and Social Services; QALY, quality-adjusted life year; STA, single technology appraisal..		

Table 49. Phillip's checklist[89]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated. A proportion of the costs in the terminal care (TC) health state was reported as paid by the voluntary sector (i.e. out of perspective), but this was shown not to influence the model results.
S3: Rationale for structure	The model structure is consistent with previously used models in advanced, previously treated RCC and has been validated by oncologists treating RCC in the UK.
S4: Structural assumptions	The chosen structure is appropriate, and reflects the clinical stopping rules for all the active interventions with patients being able to receive treatment after progression.
S5: Strategies/ comparators	Nivolumab was compared to axitinib, everolimus and best supportive care (BSC).
S6: Model type	Appropriate but not clearly stated. The model was based on the area under the curve (AUC) approach; however, the company stated that a Markov model was used.
S7: Time horizon	A lifetime horizon of 30 years was used, considered sufficient to capture all the relevant costs and benefits associated with advanced, previously treated RCC.
S8: Disease states/pathways	The model included six health states: progression-free survival on treatment (PFST), progression-free survival off treatment (PFSN), post-progression survival on treatment (PPST), post-progression survival off treatment (PPSN), terminal care (TC), and death. The health states considered are deemed appropriate and sufficient to capture all the outcomes and costs.
S9: Cycle length	Weekly cycles were chosen, deemed appropriate by the ERG. No half-cycle correction was applied due to the short length of cycles.
Data	
D1: Data identification	The company states that there was insufficient time to carry out systematic reviews, as this single technology appraisal (STA) was originally part of multiple technology appraisal (MTA), and the change did not allow sufficient time for the company to perform a full systematic review. However, the company referred to the literature searches carried out as part of TA 333, and also carried out a targeted search to identify data on adverse events.[78]
D2: Pre-model data analysis	The survival analysis that was carried out for the head-to-head trial data for nivolumab and everolimus was extensive and well reported. The ERG notes that the company used the proportionality of the hazards as a decision criterion while performing analyses using

Dimension of quality	Comments
	regression models which do not make use of the proportional hazard (PH) assumption; furthermore, the accelerated failure time (AFT) or proportional odds (PO) assumptions underlying non-PH models were not explored when assessing the appropriateness of AFT and/or PO models. A network meta-analysis (NMA) was carried out to obtain hazard ratios (HRs) for PFS and OS for axitinib and BSC compared with nivolumab. Based on clinical opinion, the ERG disagrees with the assumption that patients in the CheckMate 025 trial and in the AXIS trial are a homogeneous population given the differences at baseline in terms of prognosis and number of previous therapies received.[37, 90] The results of the NMA showed everolimus to be more effective than axitinib; this was considered implausible and unexpected by the ERG's and the company's clinical experts. Additionally, the ERG notes that there are other theoretical issues regarding the incorporation of the NMA results into the survival results from the CheckMate 025 trial, as detailed in Section 5.5.5. The ERG does not consider the extrapolations based on the results of the NMA to be reliable.
D2a: Baseline data	The baseline characteristics of patients who enrolled in the CheckMate 025 trial were assumed appropriate for the model population. According to the ERG's clinical experts, the patients in CheckMate 025 trial had a better prognosis than previously treated advanced or metastatic RCC patients encountered in routine clinical practice in the UK. Clinical expert opinion also highlighted that the average patient profile observed in the AXIS trial was more in line with what is expected in UK routine practice. Given the difference in prognosis indicated by the clinical experts, the ERG does not consider the difference in patients' baseline health-related quality of life (HRQoL) between patients treated with axitinib and everolimus or nivolumab to be reasonable.[65]
D2b: Treatment effects	Treatment effects on OS and PFS were modelled using treatment-specific parametric curves to estimate the proportion of patients in each health state, extrapolated until the end of the time horizon. Treatment effectiveness data for nivolumab and everolimus was obtained from the CheckMate 025 randomised clinical trial.[37] A network meta-analysis was carried out to estimate the treatment effectiveness of axitinib and BSC relative to everolimus. The company assumed different relative treatment effects between nivolumab and the comparators, applying different statistical methodologies with insufficient justification. The ERG disagrees with the company's assumptions about, and implementation of, the relative treatment effects. Further details are reported in Section 5.5.5.
D2c: Costs	Treatment duration was based on time-to-discontinuation (TTD) data from the CheckMate 025 trial for nivolumab and everolimus. In the company's model, TTD determined the proportion of patients on treatment at each point in time who would accrue treatment-related costs (i.e. cost associated to drug acquisition, administration and treatment-related toxicity). In the absence of data, patients on axitinib were assumed to discontinue treatment at time of progression. The total dose of nivolumab accounted for the delayed and missed doses in the CheckMate 025 trial; the total everolimus dose was calculated based on the number of packages to be acquired based on the consumption observed in the trial. The company assumed the total quantities, and thus costs, to be discounted by 8% and 6% for nivolumab and everolimus, respectively, based on trial data. The cost of axitinib was set equal to 102% based on the drug quantity used in the AXIS trial.[37, 79] It is unclear whether the calculations were comparable between the three drugs. Additionally, the ERG notes the presence of substantial uncertainty around the assumption of a constant reduction in drug use and costs for the entire time horizon. Resource use for management of advanced RCC was assumed to be the same as that in TA333.[78] No oncologist visits were assumed in the base case, contrary to clinical expert opinion. This assumption was tested in a scenario analysis. The ERG disagrees with the inclusion of subsequent therapy costs in the model, when there are no NICE-approved third-line therapy options in the current treatment pathway in the UK. The company carried out an additional sensitivity analysis at clarification stage removing this cost and assuming that patients only received BSC. The company reported that a proportion of the cost assumed for terminal care, which was obtained from a paper published by the King's Fund, falls outside the remit of the NHS

Dimension of quality	Comments
	perspective. However, according to a scenario analysis carried out by the company at clarification stage, the entity of the non-NHS costs did not seem to have any impact on the cost-effectiveness results.
D2d: Quality of life weights (utilities)	Health state utility values (HSUVs) for patients on nivolumab and everolimus were obtained from CheckMate 025, using a mixed regression model. [37] HSUVs for axitinib and BSC were derived from the AXIS trial and extracted from TA333. [78, 79] The values used in the analyses included a disutility related to disease progression and an additive effect for treatment, assumed to include impact of drug-related toxicities on HRQoL.
D3: Data incorporation	Data incorporation was generally appropriate. The ERG identified a structural error in the integration of progression-free survival (PFS) and overall survival (OS): the proportion of patients who are alive and progression-free (i.e. PFS) was set as the lower bound for the proportion of patients alive (i.e. OS).
Assessment of uncertainty	
D4a: Methodological	Methodological and structural uncertainty was adequately explored for each individual analysis in the model. The electronic model allowed a high degree of flexibility as several options were incorporated to allow varying methodological and structural assumptions.
D4b: Structural	
D4c: Heterogeneity	The main source of heterogeneity identified by the ERG was in the difference between the populations in the CheckMate 025 and the AXIS trial, as highlighted by the ERG's clinical experts. This influenced mainly relative treatment effectiveness and treatment-specific HSUVs, explored separately by the company.[37, 90]
D4d: Parameter	Parametric uncertainty was adequately explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case.
Consistency	
C1: Internal consistency	The model was internally consistent, with the exception of the error in the integration of PFS and OS.
C2: External consistency	The ERG's clinical experts noted that the relative treatment effectiveness estimate between axitinib and everolimus was not plausible, and therefore that the company's results for the comparison between nivolumab and axitinib lacked face validity.

Abbreviations used in table: AFT, accelerated failure time; BSC, best supportive care; CS, company's submission; ERG, evidence review group; HRQoL, health-related quality of life; HSUV, health-state utility value; NHS, National Health System; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PFSN, progression-free survival "off treatment", PFST, progression-free survival "on treatment"; PH, proportional hazards; PO, proportional odds; PPS, post-progression survival; PPSN, post-progression survival "off treatment", PFST, progression-free survival "on treatment"; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; QALYs, quality-adjusted life years; RCC, renal cell carcinoma; RCT, randomised clinical trial; SmPC, summary of product characteristics; TC, terminal care.

5.5.2 Modelling approach and model structure

The ERG finds the modelling approach and model structure chosen to be appropriate, considering the decision problem and the available data. A semi-Markov area under the curve [AUC] modelling approach was taken, which the company described as, "a Markov model" (CS, pg 134, Section 5.2.2).

The partition of the PFS and PPS health states by treatment status is deemed appropriate by the ERG as the clinical stopping rules for the three active treatments allow for treatment continuation beyond progression. Additionally, the CheckMate 025 data showed that a non-negligible proportion of patients would continue to receive nivolumab treatment after progression.[37, 82, 83]

The cycle length applied in the model is considered appropriate and sufficiently short to capture accurately the expected time spent in the health states and the resources used by patients. The discounting applied to costs and QALYs was in line with the NICE Reference Case.[80] The company did not discount life years in the base case, which resulted in increased interpretability of the clinical model outcomes as it provided an easy way to compare the model results with external survival estimates.

The electronic model was generally sound and transparent. However, two modelling choices were not satisfactorily reported or justified:

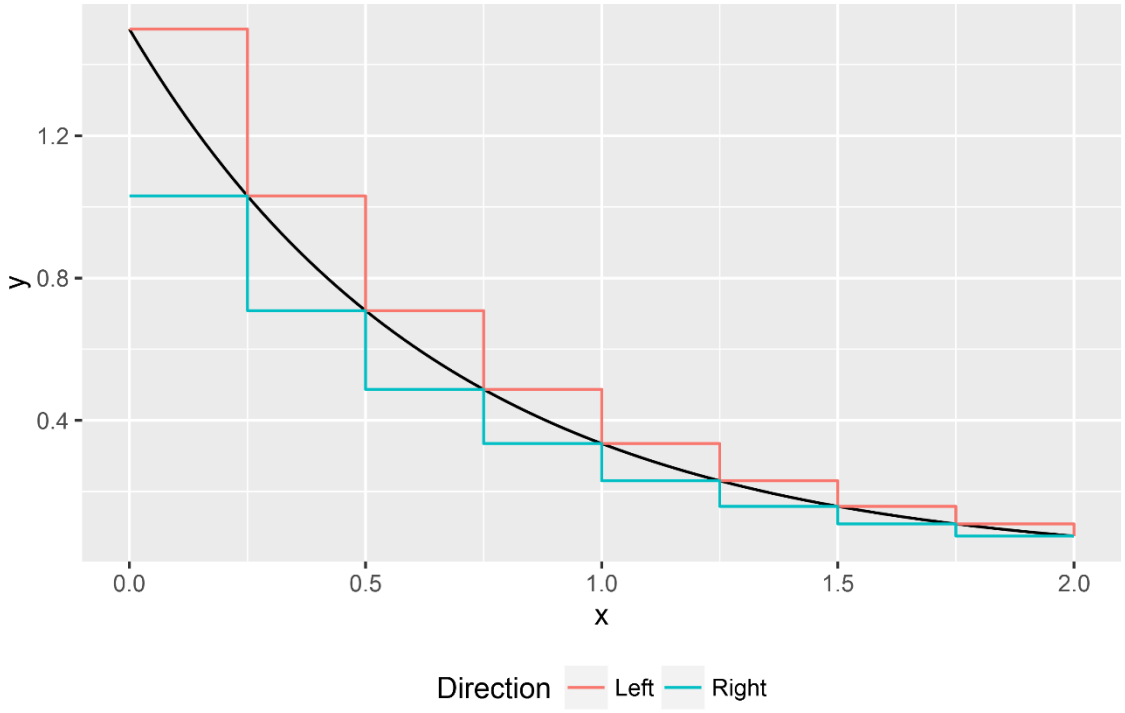
1. Direction of time discretisation;

2. Setting the number of patients alive and progression-free (i.e. PFS) as the minimum of the patients alive (i.e. OS).

5.5.2.1 Direction of time discretisation

The company discretised time using a right-direction approach, effectively estimating the areas under the curves (i.e. integrating the survival curves to estimate the mean times) using a right Riemann sum, rather than the more common left Riemann sum or the trapezoidal approach, corresponding to the half-cycle correction method. The company did not describe this approach, which is not usually adopted in AUC models, and that produces a small underestimate of the area under the curves (this in contrast with the left Riemann sum, which overestimates the areas). The difference between the two approaches is shown in Figure 36.

Figure 36. Example of left and right Riemann sums



The ERG notes that this choice does not constitute a mistake in any way, and that given the fine scale used when discretising time (i.e. weekly cycles for a lifetime horizon), the difference with a left-direction approach is expected to be almost null. However, as the use of this approach is uncommon in health economics modelling, the ERG expected the company to justify its use.

This approach implies that, at the beginning of the model, some patients are considered already dead, and thus do not accrue costs or QALYs. Using a left Riemann sum, these patients would be considered dead at the beginning of the second cycle instead.

5.5.2.2 Errors in data integration and modelling

The ERG found three issues in the approach to the integration of OS, PFS and TTD leading to errors. These depended on treatment (i.e. nivolumab and everolimus or axitinib and BSC), as the calculations were slightly different:

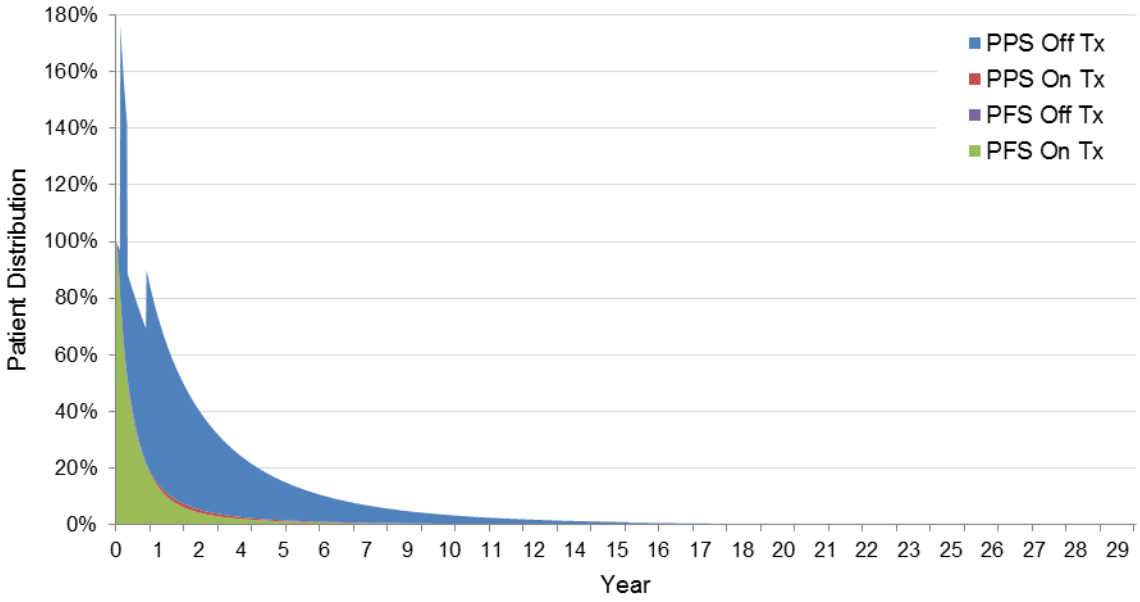
- PFS was the lower bound of OS in the nivolumab and everolimus models. This implied that the proportion of patients alive and free from progression was, in several model cycles, greater than the proportion of patients alive in the same cycle. In the company's base case, this favoured nivolumab compared to everolimus as nivolumab was associated with a greater area between the OS and PFS curves in which the PFS curve was greater than the OS. The ERG corrected the binding limiting the proportion of patients alive and not progressed to the proportion of patients alive, and not vice versa; the mean survival time removed compared to

the company's base case was 1.22 and 0.22 months (5.31 and 0.10 weeks) for nivolumab and everolimus, respectively;

- The possibility of the PFS curve being greater than OS (which was verified in the base case) was not taken into account by the company in the axitinib and BSC models. This led to negative proportions of patients in the health states of the model in correspondence of several model cycles (e.g. a negative proportion of patients was expected in the axitinib PPSN health state at cycle 1). The variation resulted in a negligible increase in the ICERs for nivolumab versus axitinib and nivolumab versus BSC. This was because the correction reduced slightly the time spent in the PFS health state while increasing by the same amount the time spent in the PPS health state for both axitinib and BSC (precisely by 0.050 and 0.002 weeks, respectively). The total time alive did not vary;

- The possibility of TTD being greater than OS and/or PFS led to errors in the estimation of the proportion of patients in the PPSN health state. The base case was not affected, but alternative scenarios resulted in errors in overestimated survival times (and thus costs) when the TTD curve was higher than OS and PFS. For example, when choosing a generalised gamma model for TTD the ICER for the comparison between nivolumab and everolimus was overestimated by £40,000 per QALY gained. A clear illustration of the error in the model predictions for everolimus when selecting a generalised gamma model for TTD is shown in Figure 37.

Figure 37. Error in estimation of proportion of patients in the PPSN health state of the everolimus arm when selecting a generalised gamma model for TTD



Abbreviation in figure: PFS, progression-free survival; PPS, post-progression survival; PPSN, post-progression survival not on treatment; TTD, time to discontinuation; Tx, treatment.

The results of the amended model are reported in Section 6.1.

5.5.3 Population

The population considered in the economic model was adults with previously treated advanced RCC, which is in line with the population specified in the NICE final scope.[23] The baseline characteristics of patients in the model were the same as patients in the CheckMate 025 trial.[37]

According to the ERG's clinical experts, and as already described in Section 4.4., patients enrolled in CheckMate 025 were considered a selected group of patients, with better prognosis than patients with advanced RCC routinely seen in UK's clinical practice. One of the ERG's clinical experts stated that patients in the AXIS trial were more representative of the UK second-line RCC patient population compared to those in CheckMate 025.

The patient populations in the AXIS trial and in CheckMate 025 were implicitly assumed homogenous in the cost-effectiveness analysis. This emerged from the approach taken by the company to estimate treatment effectiveness and HRQoL in the model. However, according to the ERG's clinical experts, the patient populations in the two trials were different. As mentioned in Section 4.4, patients in the AXIS trial had only received one line of therapy prior to enrolment while 28% of patients in CheckMate 025 received two prior therapies for advanced RCC, and the prognosis of patients at baseline was considered different by the ERG's clinical experts based on their MSKCC scores, with nearly twice as many patients in the AXIS trial falling in the "poor" risk group compared to CheckMate 025.[37, 90]

The ERG notes that the uncertainty associated with the assumption of homogeneity between the two populations would propagate to the cost-effectiveness analysis results. Treatment effectiveness estimates used in the model were based on a network meta-analysis combining the two populations. As for HRQoL, estimates were based on EQ-5D data collected in the respective trials and were used in the model without adjustments. As reported in Section 5.4.4 and Section 5.5.7.2, the HSUVs for patients receiving everolimus and axitinib were substantially different. According to the ERG's clinical experts, this difference is most likely a result of the differences between the two populations, and not due to treatment.

The ERG is uncertain of the extent of the impact of these two factors, considered associated to the heterogeneity of the populations in the two trials, on the overall cost-effectiveness results. The sensitivity of the model results to the assumption of comparability between the patients in the AXIS and CheckMate 025 trials is explored in Section 6.2.

5.5.4 Interventions and comparators

The intervention and comparators considered in the economic analysis were nivolumab, everolimus, axitinib and BSC. These are in line with the intervention and comparators included in the NICE final scope for this STA.[23]

The modelled treatment regimen was 3mg/kg IV every two weeks for nivolumab, 10 mg orally every day for everolimus, and 5 mg orally twice a day for axitinib. These regimens are in line with what was reported in the CheckMate 025 and AXIS trials, as well as the recommended doses for everolimus and axitinib and the draft SmPC for nivolumab presented in Appendix 1 of the CS.[82, 83]

The company included a reduction (or increase) factor to relate the planned and actual drug use. The proportion of planned drug dose received is discussed in Section 5.5.8.1.

Time on treatment was modelled using parametric survival models. Time-to-discontinuation (TTD) data from the CheckMate 025 trial were used for time on treatment with nivolumab and everolimus; TTD for axitinib was based on assumptions. In line with the CS, TTD is discussed as part of the treatment effectiveness in Section 5.5.5.3.

5.5.5 Treatment effectiveness

In this Section, the ERG focuses on the choice of data, extrapolation and modelling approaches chosen to model treatment effectiveness in the company's model. Treatment effectiveness determined the time spent by patients in the six health states of the model, i.e. PFST, PFSN, PPST, PPSN, TC and death. In this Section the ERG looks at the head-to-head analyses of OS, PFS and TTD data between everolimus and nivolumab in CheckMate 025 and lastly at the application of the results from the NMA to estimate the OS and PFS of axitinib and best supportive care (BSC). The ERG notes that the company's survival analysis was carried out appropriately and in general followed the recommendations of the NICE Decision Support Unit Technical Support Document 14.[91] The company reported the methods clearly and provided graphical analyses to support the modelling approaches taken.

The company used the validity of the PH assumption as a decision criterion to use dependent (i.e. parametric regression with a covariate for the treatment effect) or independent model fits (i.e. use parametric models fitted separately to the two trial arms). This might be an appropriate strategy when fitting parametric models relying on the PH assumption, e.g. exponential, Weibull or Gompertz. However, it should not influence the analysis when testing non-PH models, such as the log-logistic model. The company did not report performing tests for the accelerated failure time (AFT) or the proportional odds (PO) assumptions when fitting AFT and/or PO models. The ERG notes that the appropriateness of extrapolating long-term outcomes based on PO and AFT models was not

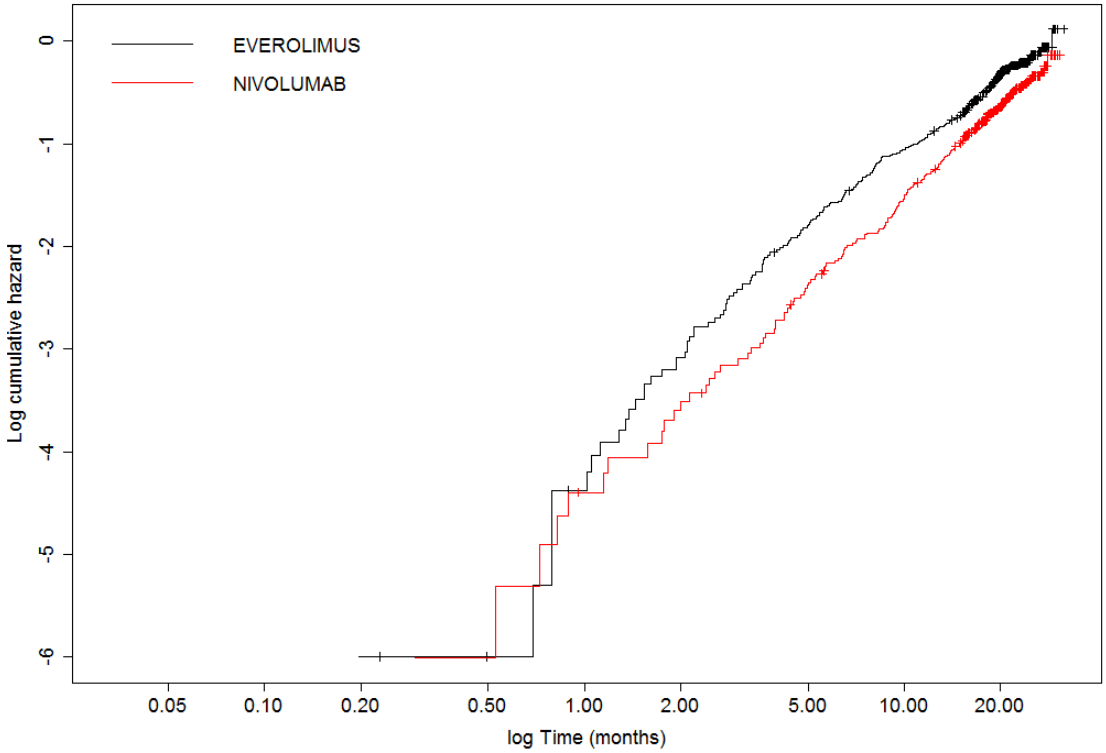
sufficiently justified, and that these potentially inappropriate effects were assumed constant over the entire time horizon.

The ERG appreciates that the company implemented in the electronic model an extremely broad set of survival models tested in the analyses. The company included both independent and dependent fits for 6 parametric models and 6 spline-based models for all outcomes, for a total of 24 models for each of the 3 time-to-event endpoints, i.e. OS, PFS and TTD. This resulted in an extremely transparent and flexible model, which allowed the ERG to conduct a broad range of sensitivity analyses around the modelling assumptions. In addition, the ERG also notes that the company managed to implement efficiently the alternatives, which did not result in slowing down the model execution.

5.5.5.1 Overall survival

The company considered the PH assumption to hold for OS, as described in Section 5.4.2.1 based on the analysis of the log-cumulative hazard plot. The ERG notes that in the log-cumulative hazard plot (Figure 38) the curves for the two treatment crossed and separated only after 1.5 months. The ERG does not consider the crossing of the curves at the end of the follow-up times to be particularly informative, given the heavy censoring in both CheckMate 025 trial arms.

Figure 38. Log-cumulative hazard plot, OS in CheckMate 025 (CS, pg 139, Section 5.3.1)

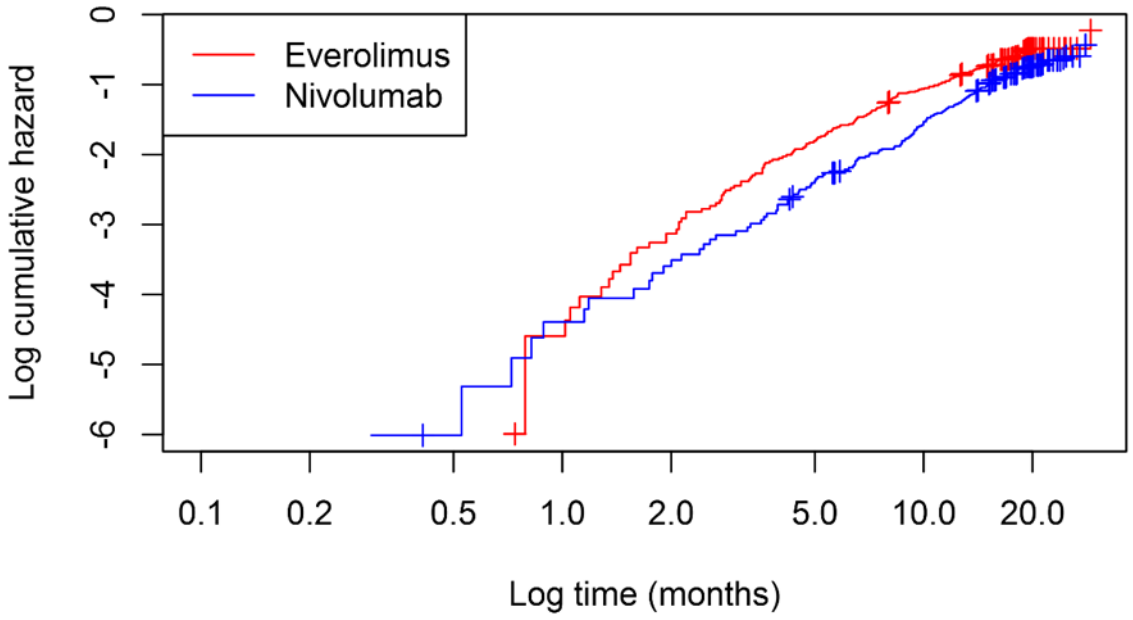


The ERG does not agree with the company's conclusion of PH from visually inspecting the log-cumulative hazard plot. This is because:

- The curves cross;
- The difference in the hazards increases until about month 2, and it seems to decrease at later times (month 10 and later);
- The KM curves (Figure 19) seem to be approximately parallel from month 8 onwards, after separation from month 0 to month 8.

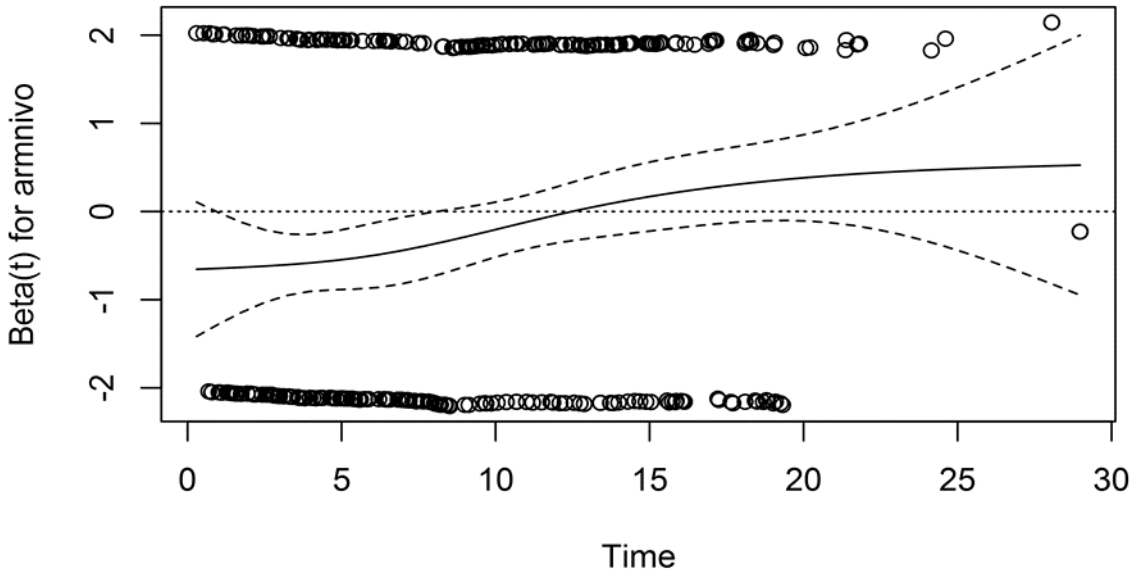
The ERG tested the PH assumption by fitting a Cox PH model to the OS pseudo-individual patient data (IPD). The pseudo-IPD were obtained from the KM estimates and the number of patients at risk in correspondence of the steps of the KM curves, which were contained in the economic model provided by the company. The Guyot *et al*. method was applied to simulate the pseudo-IPD using the algorithm in the pre-release *survHE R* package.[92, 93] The ERG notes that the simulated KM curves and the log-cumulative hazard plot, shown in Figure 39, were reasonably similar to the original ones.

Figure 39. Log-cumulative hazard plot from pseudo-OS IPD



The ERG fitted a Cox proportional hazards model and performed the Grambsch and Therneau test for the proportionality of the hazards between the treatments via the *cox.zph* function in the *R* statistical package.[94, 95] The test results indicated non-proportionality of the hazards ($\rho = 0.17$, $X_1^2 = 9.7$, $p = 0.00185$), as confirmed by the plot of the scaled Schoenfeld residuals against time shown in Figure 40. The residuals seem to indicate a linear trend over time, negating the proportionality of the hazards.

Figure 40. Scaled Schoenfeld residuals for the Cox PH model fitted to pseudo-OS IPD



The company's analysis showed that the log-logistic model was the best fit to the data in terms of AIC and BIC; however the selected curve was a generalised gamma, as, "Oncologists independently reported that log-logistic extrapolations were too optimistic and independently estimated that expected 5-year survival for such patients treated with everolimus is realistically around 10-12% […] generalised gamma and exponential models fits best approximate these 5-years survival expectations" (CS, pg 140, Section 5.3.1). The ERG agrees with the company's approach, as the validity check from clinical experts should always supersede small differences in the statistical fit to the data.

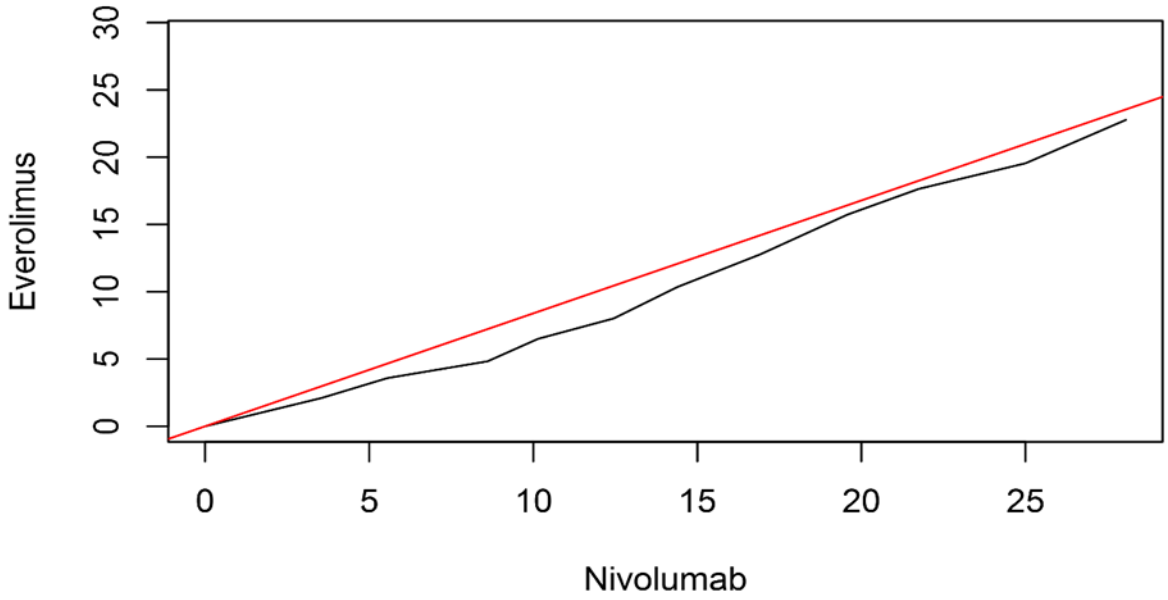
However, the ERG notes that the higher than expected projections of survival using the log-logistic model may also be caused by differences in the two populations compared, i.e. the CheckMate 025 trial patients and the previously treated advanced or melanoma RCC patients in England. This issue is explored in Section 5.5.3.

The ERG notes that both the generalised gamma and log-logistic regression models rely on the AFT assumption (in particular, the log-logistic can also be parameterised as proportional odds model). The ERG tested the AFT assumption graphically using a quantile-quantile (QQ) plot, shown in Figure 41. If the AFT assumption holds, the quantiles of survival times between the treatments should be linear over time. In the ERG's interpretation, the QQ plot seems to show a departure from the AFT assumption over the time considered horizon (up to the 55th percentile).

The QQ plot was calculated by the ERG based on the KM curves reported in the electronic model, with increments of 0.05 between quantiles of the survival times in each arm. Missing data points were

produced because the everolimus curve was more complete than the one for nivolumab. These were excluded listwise.

Figure 41. Quantile-quantile plot of survival times, CheckMate 025 OS



The QQ plot in Figure 41 did not show a substantial departure from linearity, indicating that both the log-logistic and generalised gamma models are appropriate.

The ERG explores the sensitivity of the results to alternative specifications in Section 6.2.

5.5.5.2 Progression-free survival

Based on the analyses performed by the company, the ERG agrees that the Royston and Parmar spline-based models are a reasonable option to parametric models to analyse the CheckMate 025 trial PFS data.[81, 96] The ERG considers the spline-based approach in line and supported by the company's clinical reasoning. The improvement in the curve fit to the data is thought to be in accordance to the different mechanism of action and the different nature of the two treatments. In conclusion, the ERG considers the assumption of a time-varying relative effect for progression to be reasonable, with particular reference to the issue of evaluation of progression for immunotherapies using the RECIST criteria.

As the company did not report the locations of the knots in the models nor provided the code used to perform the analyses, the ERG assumed that these would be placed in the default locations chosen by the statistical package used, i.e. *flexsurv*. The program chooses the knot locations, "from quantiles of the log uncensored death times".[96] Similarly, the splines were assumed to be function of the logarithm of time, and not modelled with an absolute time scale.

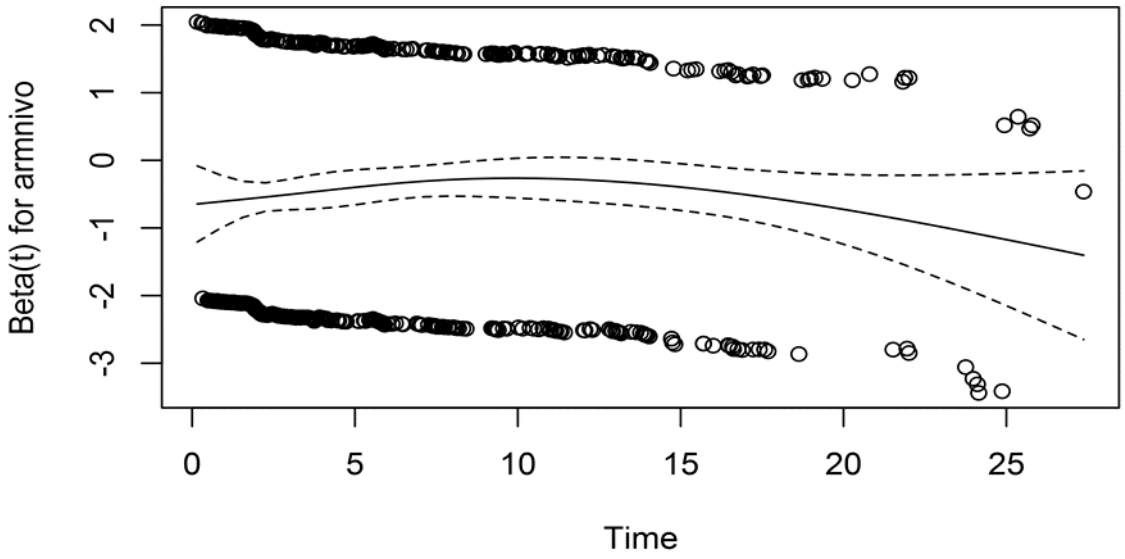
The ERG agrees with the company that the spline-based models provide a substantially better fit to the data than the parametric models, as supported by the lower AIC and BIC statistics reported in Table 32 and Table 33. The ERG is satisfied with the fit of the models to the Kaplan Meier data, even though the analysis is hindered by interval censoring as also noted by the company.

5.5.5.3 Time to discontinuation

The company applied the Royston and Parmar spline-based models to the TTD CheckMate 025 data, "following the same rationale used in the PFS analysis" (CS, pg 156, Section 5.3.3), and based on their superior fit in terms of AIC and BIC statistics, reported in Table 35. However, the company recognised that, "The standard parametric models provide a reasonable visual fit to the TTD data, compared to the PFS data" (CS, pg 156, Section 5.3.3).

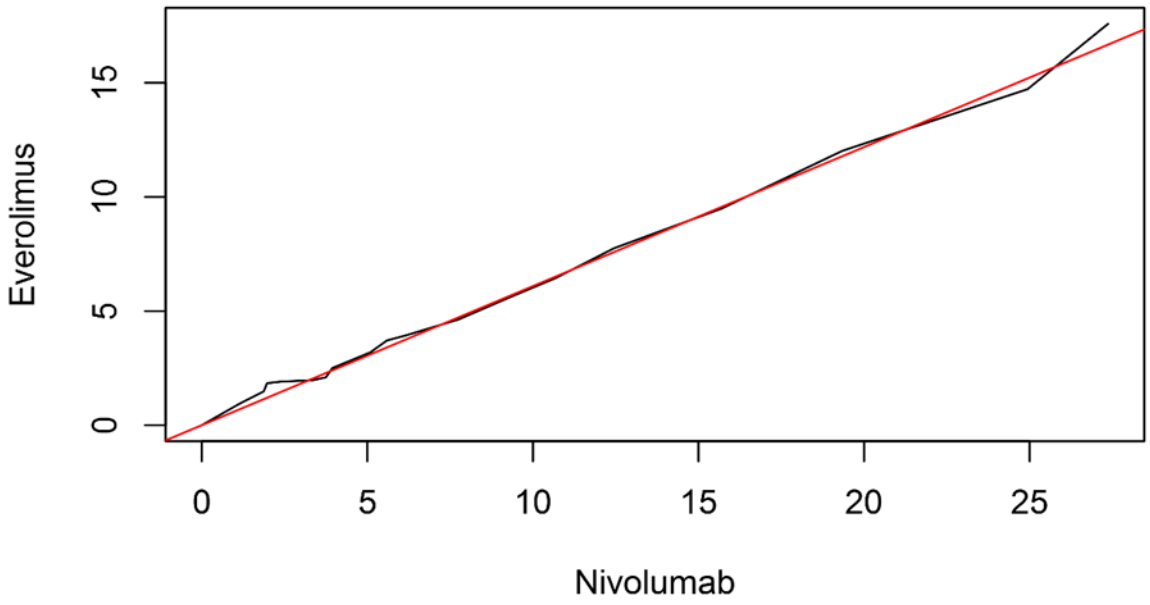
The company's rationale for fitting dependent models was based on the PH assumption, which was considered, by the company, to hold even though the log-cumulative hazard plot showed crossing curves. The ERG replicated the analysis performed for OS (described in Section 5.5.5.1) and fitted an un-stratified Cox PH model with treatment arm as a covariate and the scaled Schoenfeld residuals were analysed to evaluate the proportionality of the hazards. The data were very close to being complete, with KM estimates equal to 0.09 and 0.04 at the end of the follow-up for the nivolumab and everolimus arm, respectively. The scaled Schoenfeld residuals plot resulting from the Cox PH model is shown in Figure 42. The plot does not seem to suggest any particular deviation from the PH assumption, as confirmed by the Grambsch and Therneau test ($\rho = 0.319$, $\mathrm{X}_1^2 = 0.681$, $p = 0.409$), confirming the company's conclusion based on the visual analysis of the log-cumulative hazard plot.

Figure 42. Scaled Schoenfeld residuals for the Cox PH model fitted to pseudo-TTD IPD



The ERG also notes that the AFT assumption seems to hold for the TTD data, as shown by the straight line in the quantile-quantile (QQ) plot in Figure 43 between the two treatment arms.

Figure 43. Quantile-quantile plot of survival times, CheckMate 025 TTD data



The company does not justify the choice of the shape used to model TTD. The choice of more flexible models was supported by clinical reasons for PFS, however these could not be considered valid for TTD, as discontinuation was assumed independent on PFS. The appropriateness of the PH and AFT assumptions suggest that simpler models could be suitable to model the data compared to the Royston and Parmar spline-based models.

The goodness of fit statistics reported by the company in Section 5.3.3 of the CS showed that the generalised gamma and log-normal models were the best-fitting models in terms of AIC and BIC, respectively. The difference between the AIC and BIC measures between the models were negligible, as showed in Table 35. Visual assessment of the models fit to the KM curves is shown in Figure 44; the ERG compared the best-fitting spline model and the two best-fitting parametric models (as the AIC and BIC were not in agreement). From the comparison of the three curves it can be seen that the generalised gamma and log-normal curves are generally similar, although the former present heavier tails. However, the two parametric curves behave differently from the spline-based model, in particular in the fit to the nivolumab data.

Figure 44. Model fits to CheckMate 025 TTD data

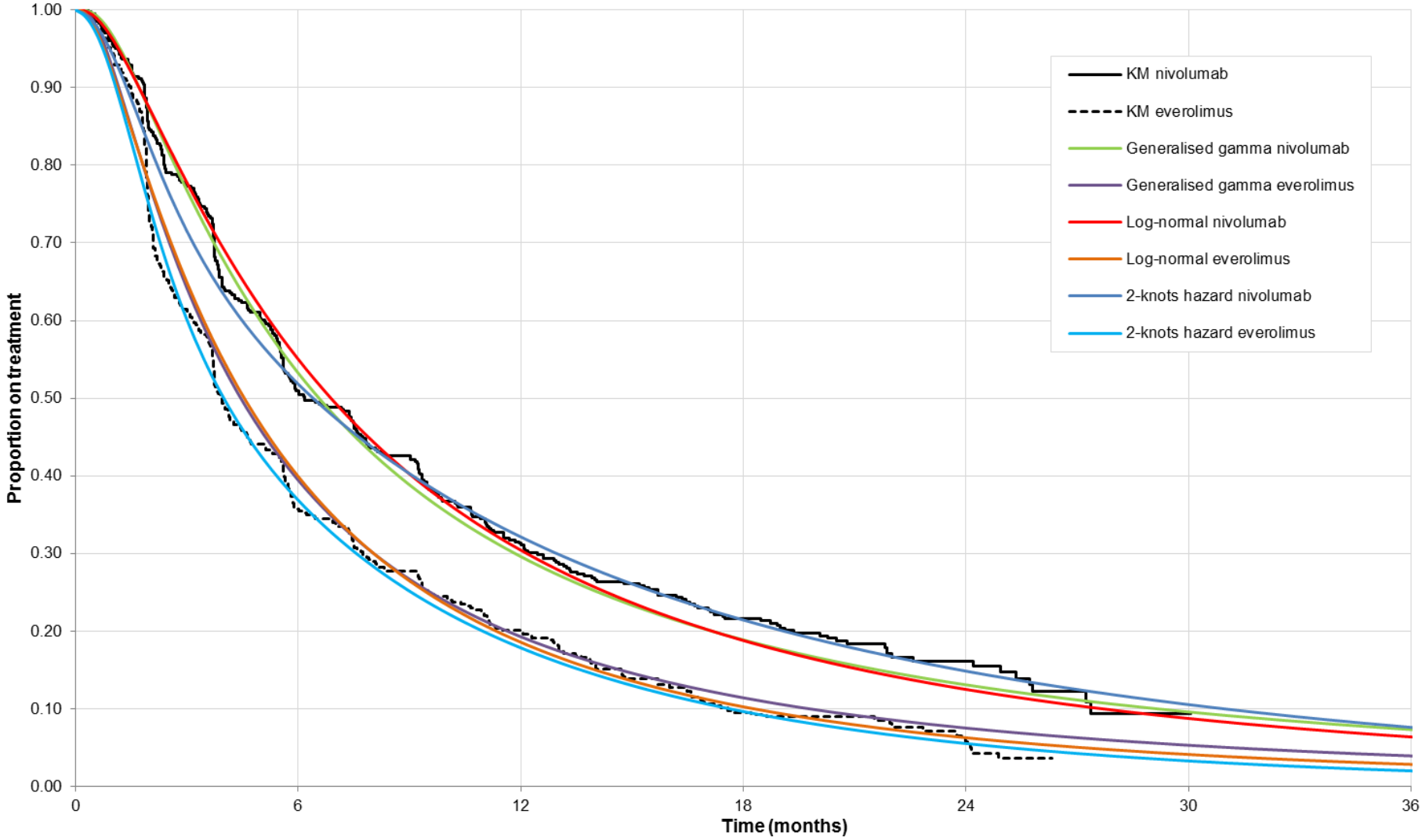
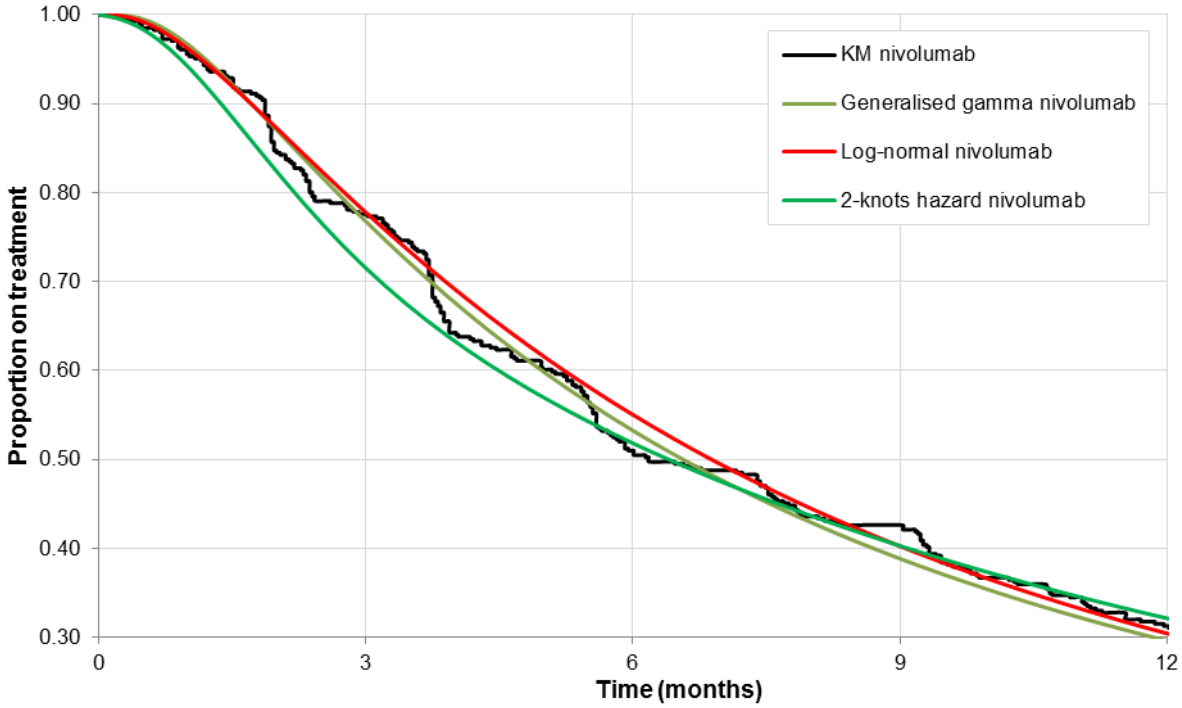


Figure 45 shows the model fit to the nivolumab TTD data for the first year of CheckMate 025, using a generalised gamma and a log-normal distribution. The ERG notes that the models are very different between month 2 and 6, with differing estimates of up to almost 10% in the proportion of patients on treatment. Given that TTD is a very influential driver of costs in the economic model and that a difference of this magnitude was not observed for the everolimus data, the ERG notes that the choice of the curves is very likely to have a noticeable impact on the model results.

Figure 45. Model fit to CheckMate 025 TTD nivolumab data, months 0 to 12



Note: the y axis starts from 0.30 and not 0.00 for ease of analysis.

The ERG explored the impact of using alternative TTD models on the economic results, and found that these, as expected, had an important impact on the ICERs. The impact of alternative TTD modelling was not explored in the company's sensitivity analyses. Alternative models for TTD are explored in the ERG's sensitivity analyses in Section 6.2.

The company assumed that, "in the absence of TTD data for axitinib, axitinib treatment was assumed to continue until disease progression" (CS, pg 159, Section 5.3.3). Considering that almost no difference was observed between TTD and PFS for everolimus in CheckMate 025, and that the two treatments are expected to have similar discontinuation rules, the ERG considers this assumption appropriate and reasonable.

5.5.5.4 Incorporation of NMA results to estimate axitinib and BSC OS and PFS

The clinical opinion sought by the ERG suggested that the comparative OS between axitinib and everolimus estimated by the company lacked face validity. The experts independently agreed on the non-inferiority of axitinib compared to everolimus, both in terms of OS and PFS. The company

acknowledged that the results from the NMA produced results not in line with the expectations of the clinical experts interviewed, as reported in Box 10.

Box 10. Company's comments on the superior efficacy of everolimus over axitinib resulting from the NMA

[…] at clinical review, oncologists did not anticipate a survival advantage of everolimus over axitinib, while recently published evidence suggests similar progression-free survival across axitinib and everolimus in advanced RCC patients previously treated with sunitinib.
Abbreviations in box: RCC, renal cell carcinoma.

The ERG considers the application of the OS NMA HRs to produce implausible results in the economic model based on the clinical experts' consensus on lack of face validity for the comparison between everolimus and axitinib. In addition, the ERG also considers that further modelling and statistical issues remove validity from the company's analysis of both PFS and OS.

To estimate the treatment effectiveness associated to axitinib and best supportive care (BSC), the company applied the HRs estimated from the NMA results, described in Section 4.4. The crossover-adjusted HRs were selected for the OS; the company stated that this choice was, "in line with NICE DSU TD16" (CS, pg 144, Section 5.3.1). However, the company did not provide further details on the nature and plausibility of the crossover adjustments performed.

The ERG notes that by applying the HRs to estimate and extrapolate relative treatment effectiveness, the company implied that:

1. The hazards between everolimus, axitinib and BSC treatments are assumed proportional; however, they are not proportional between nivolumab and the other comparators (as modelled using non-PH models for both OS and PFS). No evidence was presented to support the different relative treatment effectiveness between the treatments, and the assumption was not stated;

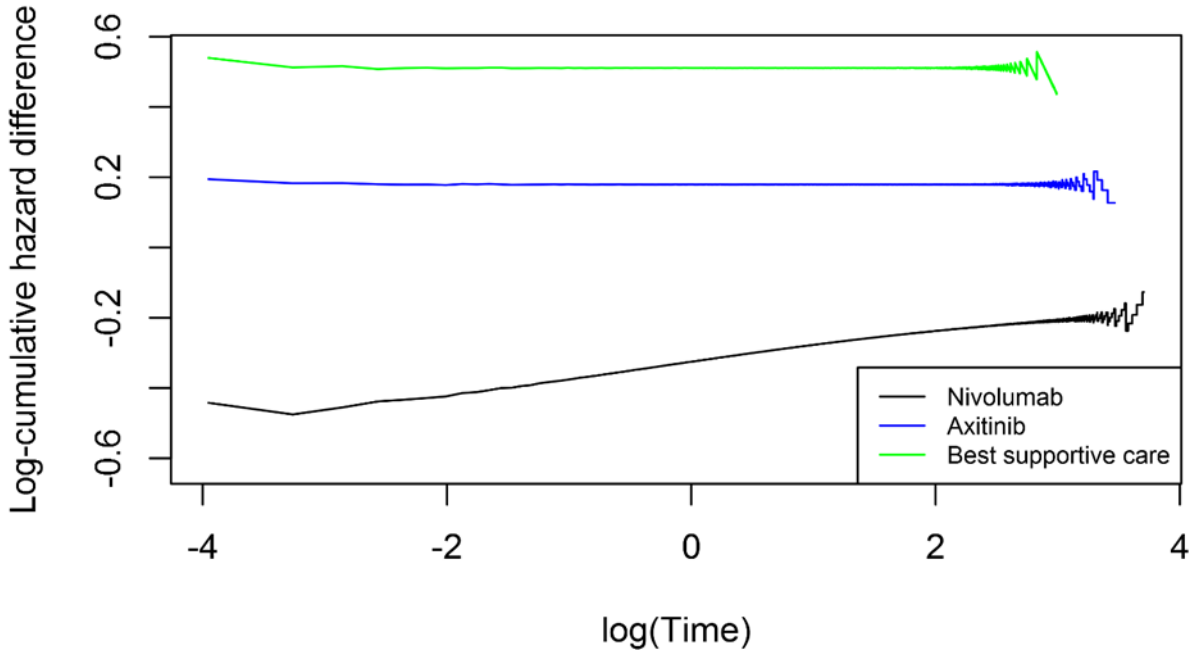
2. The relative effectiveness between treatments (i.e. HRs) are assumed constant over the entire time horizon between everolimus, axitinib and BSC. This implication is associated with substantial uncertainty. This should have been explored assuming, for example, declining relative effectiveness over time;

3. PFS and OS associated to axitinib and BSC are not expected to follow the same survival function as everolimus because the HRs were applied to non-PH models. The resulting curves might be not comparable.

The ERG notes that the proportionality of the hazard is the assumption associated with the highest uncertainty in the company's analysis, and is expected to have a major impact on the model results. The hazards were postulated proportional in the NMA, and the assumption was propagated to the economic models without providing supporting evidence.

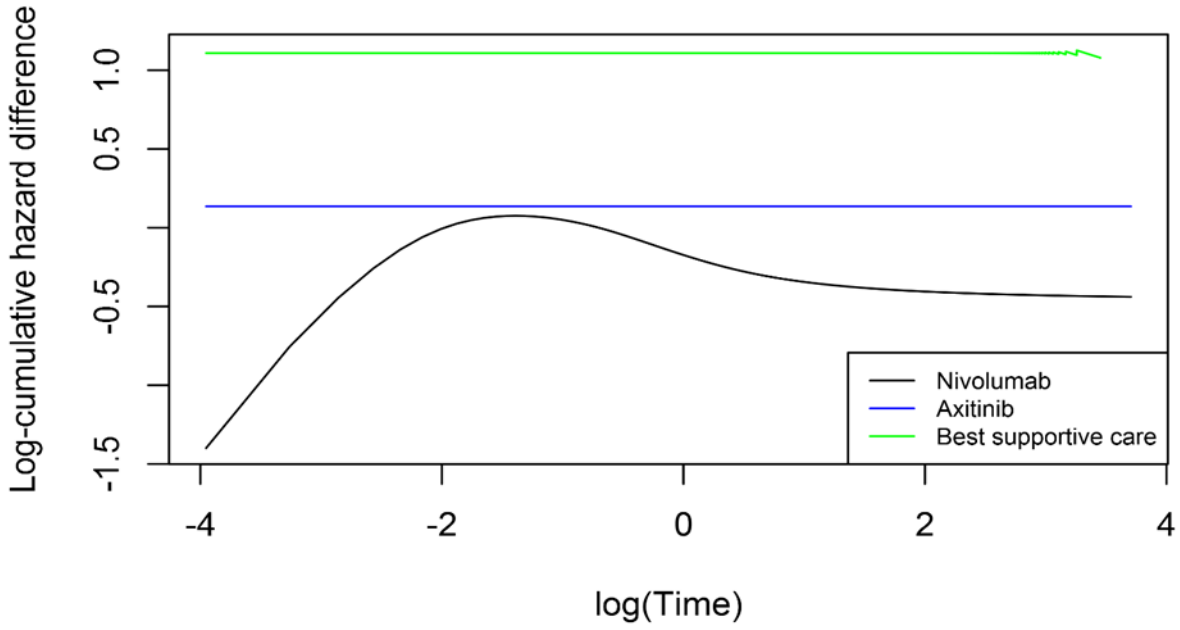
The different assumptions around relative treatment effects, and how they were implemented in the company's model, are exemplified in Figure 46 and Figure 47. The curves represent the log-cumulative hazard difference versus everolimus for the three curves used by the company for OS and PFS in the base case model, respectively. Under the PH assumption, the lines should be horizontal.

Figure 46. Differences in log-cumulative hazards compared to everolimus, company's base case OS survival models



The curves relative to the difference between axitinib and everolimus, and everolimus and BSC are clearly showing proportionality of the hazards over the entire horizon. This assumption, however, was imposed by the company and not derived from the data. The curve associated to the comparison between nivolumab and everolimus clearly shows that the hazards were not proportional, as non-PH models were used.

Figure 47. Differences in log-cumulative hazards compared to everolimus, company's base case PFS survival models



The company did not explore any of the three implications listed above. In particular, the ERG notes that the application of HRs to non-PH models is theoretically incorrect: this is because the application of HR to a PH model results is a model from the same family, but this is not guaranteed otherwise (except for the special case of a HR of 1). This applied to both PFS and OS, and it is in contrast with the NICE DSU TSD 14, which states that, "fitting different types of parametric model to different treatment arms would require substantial justification, as different models allow very different shaped distributions"[a] and also, "care should be taken that only the HR obtained from the chosen parametric model is applied to the control group survival curve derived from the parametric model fitted with the treatment group as covariate – it is theoretically incorrect to apply a HR derived from a different parametric model, or one derived from a Cox proportional hazards model" (pg 18–19).

In conclusion, the ERG does not consider the application of the NMA results in the economic model to produce reliable estimates. In the ERG's opinion, the company failed to provide supporting evidence for the many assumptions made resulting in extremely high methodological and parametric uncertainty, which was not accounted for.

The impact on the economic conclusions of alternative assumptions on the relative effectiveness of axitinib and BSC compared to everolimus and nivolumab is explored by the ERG in Section 6.2.

[a] The ERG considers that "substantial justification" is required even though the different models are not used to fit the data but to extrapolate it, in particular considering the long time horizon.

5.5.5.5 Considerations on treatment effectiveness of subsequent lines of therapy

Patients in the CheckMate 025 could, and did, receive subsequent lines of therapy beyond nivolumab or everolimus. The company stated that, "Second-line patients in CheckMate 025 and in clinical practice may go on to receive subsequent active therapy" (CS, pg 181, Section 5.5.5). However, there are no approved and reimbursed third-line treatments for RCC in England. The ERG's clinical experts confirmed that clinical practice is in line with published guidance, and that patients are not treated beyond second line but are kept on palliative care (PC) or BSC. They also stated that no clinical benefits are expected for active treatment in third-line compared to PC or BSC.

The company did not look at the potential effect, if any, of third-line therapies received in the trial. Based on clinical expert opinion, the ERG assumes no additional efficacy over PC or BSC.

5.5.6 Adverse events

The company reported any Serious Grade III/IV treatment-related adverse event (TRAE) that occurred in more than 1% of patients in either arms of the CheckMate 025 trial. These were pneumonitis, diarrhoea, anaemia and pneumonia. The rate and duration of adverse events were based on data collected in CheckMate 025. [39]

The ERG's clinical experts confirmed that all relevant treatment related adverse events that are seen in general practice have been included. However, one expert stated that although Grade II adverse events are not usually included in economic analyses, persistent Grade II diarrhoea and pneumonitis may have a considerable impact on patients' HRQoL as well as treatment continuation.

The ERG considers the approach taken to incorporate TRAEs in the model to be reasonable. However, the ERG notes that there was confusion between "treatment-emergent" and "treatment-related" adverse events between Section 4.12 and Section 5.4.3 of the CS. Treatment-emergent adverse events (TEAEs) include any event related temporally to the administration of the drug; TRAEs are a subset of AEs, which include events that can be considered causally related to the treatment administered.

The selection of a restricted set of events such as the Serious Grade III or IV TRAEs might have caused an underestimation of the total impact of treatment on HRQoL and management costs, as other adverse events with a potentially significant impact on HRQoL were not considered, i.e. Serious Grade IV TEAEs, or non-serious Grade IV TRAEs. In the ERG's opinion, a more accurate prediction of this impact would have been possible by considering, for example, Grade III or higher TEAEs. However, the ERG does not expect that considering a different set of events would have a substantial impact on the ICER, as the management costs and toxicity-related HRQoL impacts were relatively not

influential when compared to differences between treatments in terms of drug acquisition and administration costs and efficacy profiles.

The ERG identified a discrepancy between the reported number of patients in the everolimus group who experienced Grade III/IV pneumonia in the CheckMate 025 CSR, and the number of patients reported in the model. One patient who experienced Grade V pneumonia was included in the model despite the company reporting that only patients with Grade III/IV events were included in the economic analysis. The ERG notes that this minor discrepancy had no impact on the results, and that considering the event was appropriate.[39]

5.5.7 Health-related quality of life

5.5.7.1 EQ-5D data analysis

The HSUVs in the model for PFS and PPS were based on EQ-5D data collected from two trials; CheckMate 025 for nivolumab and everolimus, and the AXIS trial for axitinib and BSC.[79]

The data collected in CheckMate 025 were analysed by the company using a linear mixed model with fixed covariates for the effects of progression status, treatment allocation, and the interaction between treatment arm and progression status and with a random effect for subject. The ERG notes that the company provided the EQ-5D questionnaire completion rates in Section 5.4.1 of the CS, and additional descriptive statistics in Appendix 6 of the CS. However, no details of goodness of fit tests for the statistical model were provided in the CS. Some details on the relative goodness of fit of the selected model compared to a very limited set of alternatives were provided at the clarification stage.

The ERG notes that the company did not provide any justification for the inclusion of an interactive effect between treatment allocation and disease progression status in the HRQoL model, despite this being a non-statistically significant parameter (p=0.654), as shown in Table 50. The company only stated that, "For post-progressive patients, clinicians reported that higher utility is expected for nivolumab patients, due to both (i) treatment continuing beyond progression in many cases, and (ii) the immune-response mechanism of nivolumab that implies benefit beyond RECIST-defined progression and beyond treatment continuation" (CS, pg 165, Section 5.4.1).

However, the effect included in the model seems to contradict the company's statements, as it indicates that the HRQoL of patients who progressed in the nivolumab arm worsened more than in patients who progressed after treatment with everolimus, *coeteris paribus*. The ERG notes that the impact of this interactive effect is expected to be negligible given its effect size.

In the ERG's opinion, even though some patients might experience clinical benefit beyond RECIST-defined progression, a prolonged time on treatment would increase the effects of treatment-related

toxicities on patients' HRQoL. Given the potential effect of continuation of treatment beyond progression, the ERG asked the company to perform additional analyses on the CheckMate 025 EQ-5D data, including treatment status (i.e. on- or off-treatment). In particular, the ERG asked the company to, "adopt a stepwise variable selection approach starting from the full model [including treatment allocation, disease progression status and treatment status] and, documenting all steps, present the model resulting from the procedure" (clarification question B4). As a response, the company provided the results of 6 models fitted to the EQ-5D data, presented in Table 50.

The company's response lacked the reporting of the intermediate steps between models, as requested by the ERG. For example, a model including only treatment arm and progression status was not included in the comparison as a subsequent step to Model 6. Furthermore, the ERG finds the results potentially indicative of a non-null treatment status effect on patients' HRQoL, based on the results of Model 1 in Table 50. The ERG finds that the uncertainty associated to the HSUVs used in the company's base case, and thus the company's model, was increased rather than decreased based on the company's response.

Table 50. Model results from the stepwise variable selection approach to mixed model analysis of CheckMate 025 EQ-5D data (company's response to clarification question B4)

Parameters/Fit Statistics	Model 1: Full Model, Mean (SE), p-value	Model 2: Treatment Arm Dropped, Mean (SE), p-value	Model 3: Progression Status Dropped, Mean (SE), p-value	Model 4: Treatment Arm Added, Mean (SE), p-value	Model 5[2]: Treatment Status Dropped, Mean (SE), p-value	Model 6: Progression Status Added, Mean (SE), p-value
Intercept[1]	0.799 (0.021), <0.001	0.781 (0.008), <0.001	0.767 (0.007), <0.001	0.785 (0.011), <0.001	0.763 (0.011), <0.001	0.798 (0.010), <0.001
Treatment Arm (Everolimus)	-0.037 (0.015), 0.014	-	-	-0.036 (0.015), 0.013	-0.033 (0.014), 0.018	-0.036 (0.015), 0.017
Progression Status (Progression)	-0.024 (0.009), 0.008	-0.025 (0.007), <0.001	-	-	-	-0.069 (0.007), <0.001
Treatment Status (Off treatment)	-0.052 (0.014), <0.001	-0.057 (0.012), <0.001	-0.083 (0.005), <0.001	-0.091 (0.007), <0.001	-	-
Treatment Arm*Progression Status	-0.005 (0.014), 0.699	-	-	-	-	0.005 (0.010), 0.654
Progression Status*Treatment Status	-0.038 (0.017), 0.029	-0.014 (0.014), 0.312	-	-	-	-
Treatment Arm*Treatment Status	-0.015 (0.025), 0.543	-	-	0.018 (0.010), 0.083	-	-
Treatment Arm*Progression Status*Treatment Status	0.055 (0.029), 0.062	-	-	-	-	-
Goodness-of-fit statistics						
-2 Residual Log Likelihood	-5233.9	-5244.8	-5212.8	-5206.8	-5118.7	-5308.3
AIC	-5227.9	-5238.8	-5206.8	-5200.8	-5112.7	-5302.3
AICc	-5227.9	-5238.8	-5206.8	-5200.7	-5112.7	-5302.3
BIC	-5214.1	-5225.0	-5192.8	-5186.8	-5098.6	-5288.5

Abbreviations in table: AIC, Akaike Information Criterion; AICc, AIC correction; BIC, Bayesian Information Criterion; SE, standard error.

Company's notes: Generally, mixed models included EQ-5D Utility Index Score as a dependent measure, with the fixed effects of treatment arm, treatment status and progression status. Subject was treated as random effect. A compound symmetry covariance structure was used unless otherwise noted.

[1] Intercept includes nivolumab treatment arm, on treatment status and non-progression (SD/PR/CR) progression status.

Model 1 included all main effects, all 2 variable and 3 variable interactions. All subsequent models removed main effects and interactions in a stepwise manner.

[2] Model 5 used an autoregressive covariance structure.

5.5.7.2 Health-state utility values

The treatment-specific HSUVs applied in the company's base case are summarised in Table 51. These estimates suggest that:

- Even after progressing, patients on nivolumab and everolimus would enjoy a superior HRQoL than patients who have not yet progressed when receiving axitinib or BSC;
- The impact of disease progression varies across treatments, both in absolute and relative terms.

Table 51. Health state utility values by treatment

Treatment	PFS	PPS	Treatment-specific disutility due to disease progression
Nivolumab	0.7975	0.7281	-0.0694 (-8.7%)
Everolimus	0.7618	0.6970	-0.0649 (-8.5%)
Axitinib	0.6920	0.6100	-0.0820 (-11.9%)
BSC	0.6920	0.6100	-0.0820 (-11.9%)
Abbreviations used in the table: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival.			

The ERG's clinical experts stated that the difference in both pre-and post-progression survival utility values between everolimus and axitinib is implausible, and is likely to be a reflection of the different baseline characteristics of patients in the trials, as already noted in Section 5.5.3.

The company assumed that the HRQoL of patients receiving BSC was comparable to that of patients receiving axitinib; this was justified by the fact that the toxicity experienced when taking axitinib offsets the benefits of treatment. The assumption is deemed reasonable by the ERG in light of the clinical experts' feedback and in line with the assumptions in TA333.[78]

The ERG considers the assumption that utility decrements due to Serious Grade III/IV TRAEs were captured within the HSUVs to be reasonable. The company tested this assumption in a scenario analysis as reported in Section 5.6.2, which revealed that adding a utility decrement for TRAEs in the model had a minimal impact on the cost-effectiveness results. However, the ERG notes that this might have been caused by the restriction to a very specific category of adverse events (i.e. Serious Grade III/IV TRAEs), as discussed in Section 5.5.6.

5.5.8 Resources and costs

The ERG identified minor discrepancies between some of the unit costs reported in the CS, and the values in the sources cited. The ERG corrected the values in the model as reported in Section 5.4.7.[86] The ERG checked that the prices were correctly inflated when necessary and that discounting was

correctly applied. The following subsections detail the main issues identified in the estimation of resource use and costs in the model.

5.5.8.1 Dose calculations

The company included a reduction (or increase) factor to relate the planned and actual drug use for nivolumab, everolimus and axitinib. The dose reduction factors (i.e. administered dose divided by the suggested dose) applied in the company's base case are reported in Table 52.

Table 52. Treatment-specific dose reduction factors applied in the company's base case

Treatment	Dose reduction factor	Source
Nivolumab	92.425%	CheckMate 025 trial [39]
Everolimus	94.240%	CheckMate 025 trial[39]
Axitinib	102.000%	AXIS trial [78]

The dose reduction factors for nivolumab, everolimus and axitinib were assumed not to vary during the entire time horizon; however, the company did not provide evidence supporting this assumption. The ERG notes that the presence of time-dependent trends in dose reduction (or increase) might be influential on the models results, because the number of patients treated varies over time. Therefore, a constant reduction in costs, as assumed in the company's base case and effectively corresponding to a price discount, would yield different results than a time-dependent dose reduction factor. However, the magnitude of this difference is unknown.

Finally, it was assumed that there is a constant reduction in doses administered of nivolumab and everolimus, even though no justification was provided for this assumption. As drug costs contribute greatly to the overall costs associated with the various comparators, it is important to ensure that the assumptions made surrounding the dosage are consistent and justified. Therefore, the ERG explores the impact of assuming that patients receive 100% of planned nivolumab and everolimus doses in a scenario analysis in Section 6.2.

The dose reduction factor applied to the nivolumab dosage was described as, "calculated […] based on the proportion of doses delayed (5.075% […]) and the proportion of doses omitted (2.5%)" (CS, pg 174, Section 5.5.2). The company did not provide details on why the doses were omitted and how they were calculated. It is also unclear whether the potentially varying dosage of nivolumab, based on patients' weight, was correctly accounted for in the calculations in the denominator of the proportion. An additional source of uncertainty is how dose delay was defined and whether the delayed doses were eventually received by patients, as if that was the case their cost should not have been excluded.

The average dose received of everolimus in the CheckMate 025 trial was reported to be calculated as, "[…] the sum product of number of packs required to cover sum days of tablets received and maximum number of 28-day treatment pack cycles on treatment was calculated" (CS, pg 174, Section 5.5.2). No details were provided regarding delays or omissions in doses.

A dose reduction factor equal to 102% was assumed for axitinib, as reported in TA 333.[78] The ERG is uncertain whether the method of calculation is comparable to that of nivolumab and everolimus as this was not clearly reported in the CS. However, clinical experts sought by the ERG confirmed that this assumption is reasonable, as there is a tendency to treat patients with the highest possible dose they can tolerate.

In conclusion, the ERG is uncertain whether the dose reduction factors applied to the three active treatments are appropriate and comparable. The assumptions associated with the highest uncertainty are the removal of the delayed doses from the nivolumab acquisition costs and the assumption of a constant reduction (or increase) in the doses over time. Alternative assumptions are explored by the ERG in Section 6.2.

5.5.8.2 Resource use for health state cost estimation

The company did not consider oncologist visits in the pre-and post-progression states in the base case analysis. However, a scenario analysis was carried out to include consultant visits during pre-progression, in line with the company's and the ERG's clinical experts. In this scenario, the company assumed that patients would visit an oncologist and have blood tests corresponding to treatment administration schedule (every 2 weeks for nivolumab, and every 4 weeks for everolimus and axitinib). In the company's scenario analysis, the ICERs increased by £800, £1,741 and £79 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively, when compared to the base case estimates.

One of the ERG's clinical experts stated that patients are seen by oncologists also after progressing, and sometimes more frequently than before progression. The ERG did not explore this further as reliable estimates of the frequency of the visits during post-progression could not be obtained and because the impact on the ICER was expected to be minimal.

The company based the terminal care (TC) costs on an estimate obtained from a paper published by the King's Fund, caveating that, "Not all of these costs are direct NHS costs – some fall on 'third sector' healthcare organisations" (CS, Section 5.5.5, pg 184). The ERG requested further information at the clarification stage regarding the portion of the total costs that fall outside the direct remit of the NHS. The company's response is reported in Box 11.

Box 11. Company's response to clarification question regarding terminal care costs (company's response to clarification question B7)

The King's Fund study estimate of the cost of terminal care for UK cancer patients (£5,401 in 2007/8; £6,160 after adjusting to 2014/15 costs) is reported in a retrospective descriptive analysis of the impact of services introduced in 2004 to increase choice at the end of life for cancer patients in Lincolnshire. Parts of these services are funded by the voluntary sector, though the proportion of the total cost attributable to the voluntary sector is not reported. Using the total cost estimate can be considered appropriate because the voluntary sector are arguably picking up responsibility that falls within the remit of the NHS/PSS. Furthermore this estimate has been used to inform decision making in numerous previous NICE TAs, including TA359, completed in 2015.

Abbreviations in box: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; TA, technology appraisal.

At clarification stage, the company was asked to carry out an additional scenario analysis to test the sensitivity of the model results to variation in the TC costs. The results presented in Table 53 are based on a scenario assuming that only 50% of the King's Fund cost estimate includes costs incurred by the NHS and PSS. This had a negligible impact on the ICER with an increase of less than £100 per QALY compared to the base case results for all 3 comparisons.

Table 53. Scenario analysis assuming 50% of terminal care costs assumed in the model are NHS/PSS costs (company's response to clarification question B7)

Treatment	Cost	LYs	QALYs	Incremental costs Nivolumab versus	Incremental LYs Nivolumab versus	Incremental QALYs Nivolumab versus	ICER Nivolumab versus
Nivolumab	£88,582.15	3.44	2.31	-		-	-
Axitinib	£43,270.23	2.09	1.25	£45,311.93	1.35	1.07	£42,504.49
Everolimus	£36,086.76	2.55	1.69	£52,495.40	0.89	0.63	£83,930.16
BSC	£7,628.89	1.47	0.88	£80,953.26	1.97	1.43	£56,515.07

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

5.5.8.3 TRAE costs

In the absence of head-to-head data comparing the safety profiles, the company assumed that patients treated with axitinib would accrue the same total cost for the management of Serious Grade III/IV TRAEs associated to everolimus. The ERG's clinical experts noted that the main difference between the two treatments in terms of resources used for the management of adverse events is that everolimus is associated with more Grade III/IV pneumonitis events than axitinib, requiring more resources for clinical investigation, but the assumption was not considered unreasonable. The ERG notes that

alternative assumptions would have a negligible impact on the ICER because of the minor influence of TRAE on the model results, as discussed in Section 5.5.6.

5.5.8.4 Subsequent therapy costs

The company included subsequent treatment lines as part of the costs accrued by patients in the base case model. However, currently there are no approved and reimbursed treatment options beyond second line for the management of advanced RCC in England. The ERG's clinical experts confirmed that clinical practice is in line with published guidance, and that patients are not treated beyond second line but are kept on palliative care (PC) or BSC. As already mentioned in Section 5.5.5.5, the clinical experts did not expect clinical benefits for active treatment in third line compared to BSC or PC.

The ERG asked the company to carry out a scenario analysis at clarification stage to assess the impact on the model results of the costs associated to subsequent lines of therapies, assuming that patients would receive only BSC after treatment discontinuation. The results of this analysis are reported in Table 54. Compared to the company's base case analysis, the removal of costs associated to subsequent therapies costs led to an increase in in the ICERs of £1,684 and £3,185 per QALY for nivolumab compared to axitinib and everolimus, respectively. The ICER decreased by £4,279 per QALY for the comparison between nivolumab and BSC.

Table 54. Scenario analysis assuming patients only receive BSC after treatment discontinuation (response to clarification question B6)

Treatment	Cost	LYs	QALYs	Incremental costs Nivolumab versus	Incremental LYs Nivolumab versus	Incremental QALYs Nivolumab versus	ICER Nivolumab versus
Nivolumab	£85,223.35	3.44	2.31	-	-	-	-
Axitinib	£38,209.77	2.09	1.25	£47,013.58	1.35	1.07	£44,100.82
Everolimus	£30,798.76	2.55	1.69	£54,424.59	0.89	0.63	£87,014.56
BSC	£10,524.94	1.47	0.88	£74,698.40	1.97	1.43	£52,148.43

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

5.6 Results included in company's submission

5.6.1 Base case results

In this Section, the ERG presents the results of the base case analysis of the cost-effectiveness of nivolumab compared to everolimus, axitinib and BSC. The results of the pairwise analysis are presented in Table 55.

In the company's analysis, nivolumab resulted extending survival by 16, 11, and 17 months compared to axitinib, everolimus and BSC, respectively. Nivolumab increased quality adjusted life-years (QALYs) by 1.07, 0.63 and 1.43 on average when compared to axitinib, everolimus and BSC, respectively.

Table 55. Pair-wise analysis of cost-effectiveness of nivolumab versus comparators (CS, pg 191, Table 60)

Treatment	Cost	LYs	QALYs	Incremental costs Nivolumab versus	Incremental LYs Nivolumab versus	Incremental QALYs Nivolumab versus	ICER Nivolumab versus
Nivolumab	£91,352.66	3.44	2.31	-	-	-	-
Axitinib	£46,133.83	2.09	1.25	£45,218.83	1.35	1.07	£42,417.26
Everolimus	£38,920.38	2.55	1.69	£52,432.28	0.89	0.63	£83,829.24
BSC	£10,524.94	1.47	0.88	£80,827.72	1.97	1.43	£56,427.43

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

The QALY gain by health state for patients receiving nivolumab compared to axitinib, everolimus and BSC is summarised in Table 56. In the company's analysis nivolumab resulted in more QALYs accrued in all the health states relative to its comparators, and in a total gain of more than one discounted QALY relative to axitinib which, based on ERG's clinical expert opinion, is considered the most effective comparator. Most of the QALYs were accrued by patients in the PPS health state, regardless of treatment received.

Table 56. Summary of QALY gain by health state of nivolumab versus comparators (adapted from CS, pg 196, Tables 63-65)

Health state	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Increment (% absolute increment)		
					1 vs 2	1 vs 3	1 vs 4
PFST	0.69	0.39	0.45	0.14	0.29 (27%)	0.23 (38%)	0.55 (38%)
PFSN	0.22	0.00	0.07	0.00	0.22 (20%)	0.14 (23%)	0.22 (15%)
PPST	0.10	0.00	0.00	0.00	0.10 (9%)	0.10 (15%)	0.10 (7%)
PPSN	1.31	0.85	1.16	0.74	0.46 (43%)	0.15 (24%)	0.57 (40%)
Total QALYs	**2.31**	**1.25**	**1.69**	**0.88**	**1.07 (100%)**	**0.63 (100%)**	**1.43 (100%)**

Abbreviations in table: BSC, best supportive care; PFSN, progression-free survival off treatment; PFST, progression-free survival on treatment; PPSN, post-progression survival off treatment; PPST, post-progression survival on treatment; QALY, quality-adjusted life year.

The disaggregated costs by health state are presented in Table 57. Similar terminal care costs were incurred across the treatment options, as all patients eventually die in the model and are assumed to receive terminal care during the 8 weeks prior to death; slight differences were due to discounting. Costs incurred in the PFST health state were substantially higher for patients on nivolumab when compared to other treatment strategies. There were estimated cost savings of £1,795 and £1,992 in subsequent therapy costs for nivolumab compared to axitinib and everolimus, respectively.

Table 57. Incremental costs of nivolumab against comparators disaggregated by health state (adapted from CS, pg 198-199, Tables 66-68)

Health state	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Increment (% absolute increment)		
					1 vs 2	1 vs 3	1 vs 4
PFST	£62,779	£27,326	£18,871	£233	£35,453 (72%)	£43,908 (77%)	£62,546 (77%)
PFSN	£301	£0	£106	£0	£301 (1%)	£196 (0%)	£301 (0%)
PPST	£9,944	£0	£0	£0	£9,944 (20%)	£9,944 (18%)	£9,944 (12%)
PPSN	£6,658	£5,157	£6,155	£4,500	£1,501 (3%)	£503 (1%)	£2,158 (3%)
TC	£5,541	£5,727	£5,667	£5,792	-£186 (0%)	-£126 (0%)	-£251 (0%)
Subsequent therapy	£6,129	£7,924	£8,122	£0	-£1,795 (4%)	-£1,992 (4%)	£6,129 (8%)
Total costs	**£91,353**	**£46,134**	**£38,920**	**£10,525**	**£45,219 (100%)**	**£52,432 (100%)**	**£80,828 (100%)**

Abbreviations in table: BSC, best supportive care; PFSN, progression-free survival off treatment; PFST, progression-free survival on treatment; PPSN, post-progression survival off treatment; PPST; post-progression survival on treatment; TC, terminal care.

A summary of the disaggregated costs according to costs category and health state is presented in Table 58. The higher cost and the longer time on treatment associated with nivolumab (in both the PFST and PPST health states) resulted in an increase of 81%, 86% and 82% of the absolute incremental costs for treatment acquisition compared to axitinib, everolimus and BSC, respectively. Most of the costs were incurred before patients progressed. The differences in total costs were driven by the difference in drug acquisition costs. These are reflected in the differences in the PFST health state costs and subsequent therapy costs.

Table 58. Summary of costs disaggregated by cost categories within health states

Health state	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Increment (% absolute increment)		
					1 vs 2	1 vs 3	1 vs 4
Progression-free survival on treatment							
Treatment acquisition	£57,612	£26,653	£18,210	£0	£30,959 (63%)	£39,402 (70%)	£57,612 (71%)

Health state	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Increment (% absolute increment)		
					1 vs 2	1 vs 3	1 vs 4
costs							
Treatment administration costs	£4,192	£0	£0	£0	£4,192 (9%)	£4,192 (7%)	£4,192 (5%)
TRAE costs	£16	£39	£0	£13	-£23 (0%)	£16 (0%)	£2 (0%)
Disease management costs	£959	£634	£661	£219	£325 (1%)	£298 (1%)	£739 (1%)
Progression-free survival off treatment							
Disease management costs	£301	£0	£106	£0	£301 (1%)	£196 (0%)	£301 (0%)
Post-progression survival on treatment							
Treatment acquisition costs	£8,814	£0	£0	£0	£8,814 (18%)	£8,814 (16%)	£8,814 (11%)
Treatment administration costs	£641	£0	£0	£0	£641 (1%)	£641 (1%)	£641 (1%)
TRAE costs	£2	£0	£0	£0	£2 (0%)	£2 (0%)	£2 (0%)
Disease management costs	£486	£0	£0	£0	£486 (1%)	£486 (1%)	£486 (1%)
Post-progression survival off treatment							
Disease management costs	£6,658	£5,157	£6,155	£4,500	£1,501 (3%)	£503 (1%)	£2,158 (3%)
Other costs							
One-off progression costs	£0	£0	£0	£0	£0 (0%)	£0 (0%)	£0 (0%)
Subsequent therapy cost	£6,129	£7,924	£8,122	£0	£-1,795 (4%)	£-1,992 (4%)	£6,129 (8%)
End of life costs	£5,541	£5,727	£5,667	£5,792	£-186 (0%)	£-126 (0%)	£-251 (0%)
Total costs	**£91,353**	**£46,134**	**£38,920**	**£10,525**	**£45.219 (100%)**	**£52,432 (100%)**	**£80,828 (100%)**

Abbreviations in table: BSC, best supportive care; PFSN, progression-free survival off treatment; PFSN, progression-free survival on treatment; PPSN, post-progression survival off treatment; PPST; post-progression survival on treatment; TRAE, treatment-related adverse event.

5.6.2 Sensitivity analysis

In this Section the ERG presents the deterministic and probabilistic sensitivity analyses (PSAs) carried out by the company. The company provided the results of deterministic one-way sensitivity analyses and scenario analyses (DSA) in Section 5.8.2 and Section 5.8.3 of the CS for the comparison

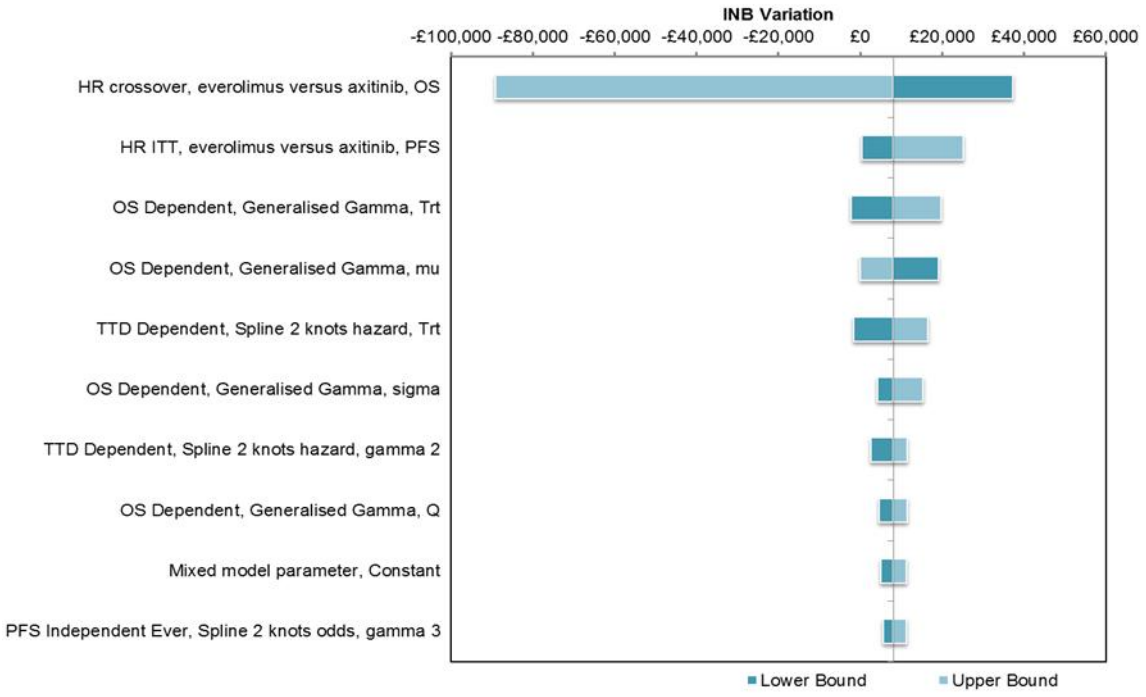
between nivolumab and axitinib. The mean results of the pairwise PSAs conducted for nivolumab against all three comparators, in addition to the cost-effectiveness plane showing the cloud of PSA simulations for nivolumab compared to axitinib, were reported in Section 5.8.1 of the CS. The DSA and PSA results for the other comparisons (i.e. nivolumab compared to everolimus and BSC) were reported in Appendix 8 of the CS.

5.6.2.1 One-way sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact on the cost-effectiveness results of the variation of the value of individual parameters. The analysis was carried out using a net-monetary benefit approach, assuming a willingness to pay (WTP) threshold of £50,000 per QALY. The results are presented in Figure 48, Figure 49 and Figure 50 for the comparisons of nivolumab with axitinib, everolimus and BSC, respectively.

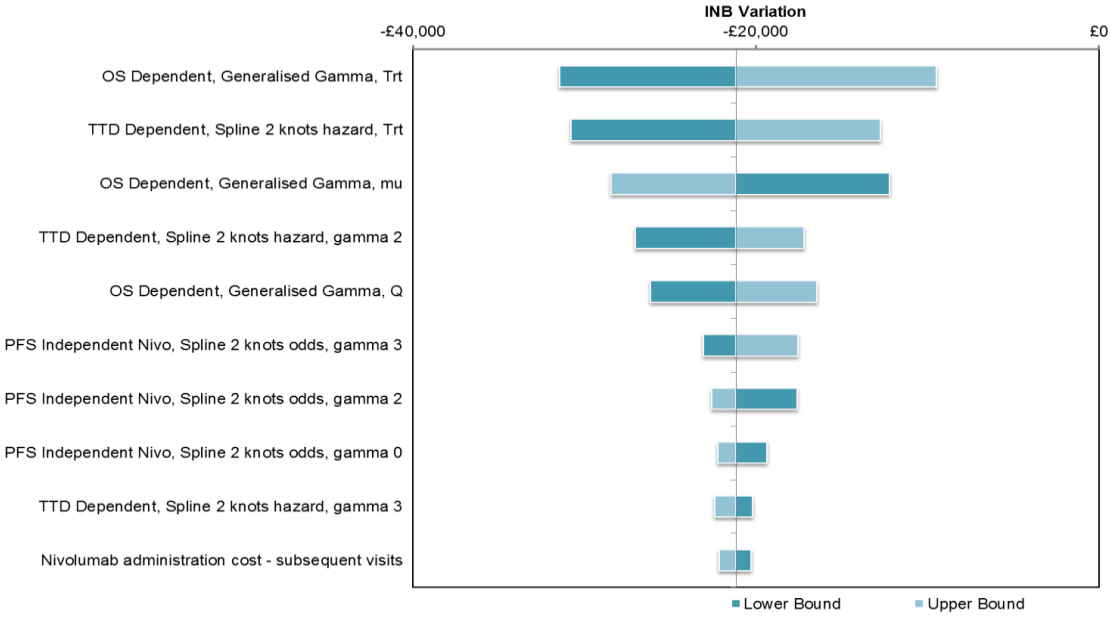
Varying the parameter estimates used to estimate the relative OS, TTD and PFS had an impact on the model results for all 3 comparisons. The results for the comparisons of nivolumab and axitinib and nivolumab and BSC were very sensitive to variations in the crossover-adjusted HR in the estimation of OS: this was because the estimate was associated with substantial uncertainty. For the comparison between nivolumab and everolimus, the most influential parameters were the model parameters used to model and extrapolate OS and TTD.

Figure 48. One-way sensitivity analysis results for nivolumab compared to axitinib (CS, pg 206, Figure 51)



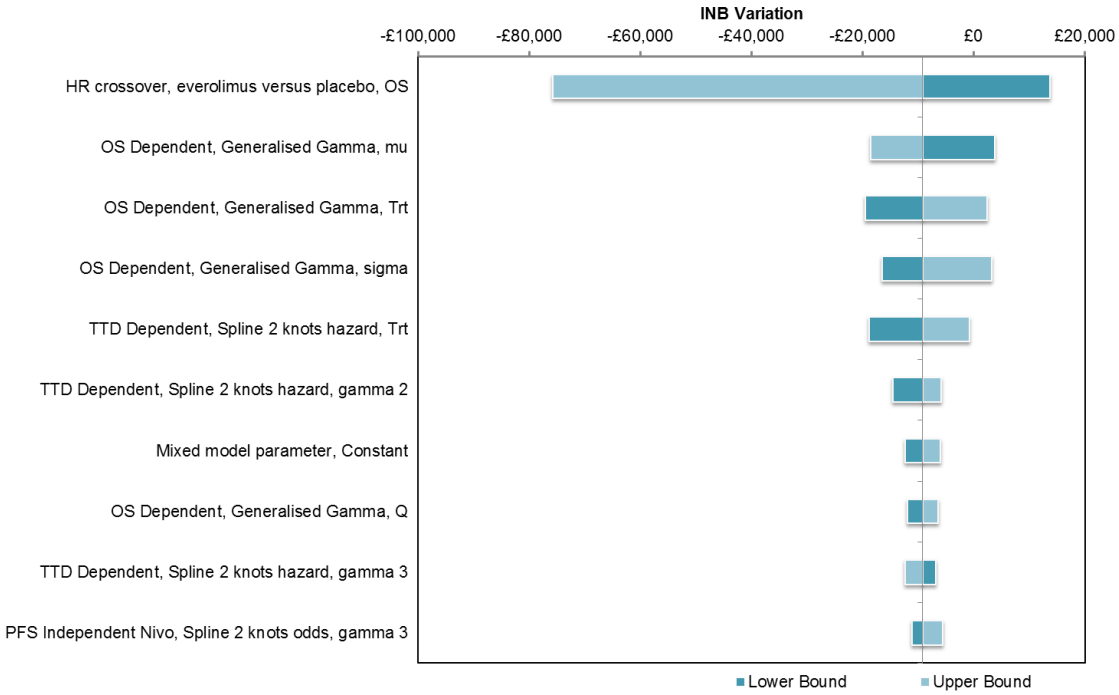
Abbreviations in figure: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation

Figure 49. One-way sensitivity analysis results for nivolumab compared to everolimus (Appendix 8, pg 110, Figure 4)



Abbreviations in figure: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation

Figure 50. One-way sensitivity analysis results for nivolumab compared to BSC (Appendix 8, pg 110, Figure 5)



Abbreviations in figure: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation

5.6.2.2 Scenario analyses

The impact of changing the following assumptions on the cost-effectiveness results of the model were assessed in scenario analyses:

- Discount rates;
- Time horizon;
- Overall survival (curve fit, and network meta-analysis assumptions);
- Utility values (values for patients on BSC, and addition of TRAE utility decrements);
- Drug related resource use (average patient weight, and vial sharing);
- Subsequent therapy costs.

The results of the company's scenario analyses are presented in Table 59. The economic model results were very sensitive to the inclusion of an immune-response effect when estimating the survival benefit for nivolumab, resulting in a reduction in the ICERs of £19,494, £51,127 and £22,947 per

QALY for the comparison with axitinib, everolimus and BSC, respectively. Using an average patient weight of 72.45kg, based on data from the Ipsos Global Oncology Monitor, resulted in a decrease in the ICERs by £6,269, £10,864 and £4,665 per QALY when nivolumab was compared with axitinib, everolimus, and BSC, respectively. The reduction in the ICERs was driven by a lower cost of the cost of nivolumab treatment, as it was the only treatment option with a weight-dependent dosage. The ERG was unable to verify this alternative value for average patient weight, as it is unclear how this data was obtained. Using the ITT NMA results had the following impact on the results for the axitinib and BSC comparisons, increasing the ICER by £9,311 and £18,956 per QALY gained for nivolumab compared to axitinib and to BSC, respectively.

Changing the assumptions around utility values for patients on axitinib and BSC had a substantial impact on the results. Taking estimates from a scenario analysis reported in TA 333 led to an increase in the ICER by £6,394 and £4,329 per QALY when comparing nivolumab to axitinib and to BSC, respectively.[78] Assuming the same utility values for axitinib and BSC as that of patients in the everolimus arm of CheckMate 025 trial increased the ICER for nivolumab compared to axitinib and BSC by £7,564 and £5,152 per QALY, respectively.[37]

Table 59. Results of scenario analysis (adapted from CS, pg 208, Table 73 and Appendix 8, pg 111, Table 16)

Parameter	Base case assumption	Scenario analysis	Nivolumab vs axitinib ICER	Nivolumab vs everolimus ICER	Nivolumab vs BSC ICER
Base case			**£42,417**	**£83,829**	**£56,427**
Discount rate (costs and utilities)	3.5%	6%	£45,407	£91,719	£60,408
Discount rate (costs and utilities)	3.5%	0%	£37,598	£71,564	£50,212
Time horizon	30 years	20 years	£43,577	£87,357	£57,570
Time horizon	30 years	25 years	£42,879	£85,282	£56,881
Time horizon	30 years	35 years	£42,100	£82,829	£56,116
OS NMA analysis choice	Crossover-adjusted	ITT	£51,728	£83,829	£75,024
OS curve choice	Generalised Gamma	Exponential	£44,069	£85,595	£58,888
Vial sharing	No	Yes	£39,947	£79,619	£54,589
Nivolumab survival benefit	No immuno-response effect	Include immuno-response effect	£22,923	£32,703	£33,481
Health state resource use	TA 333 assumptions	Clinician estimates	£41,617	£82,088	£56,348
Subsequent treatment costs for nivolumab	As per CheckMate-025	Equal to everolimus	£43,529	£85,723	£57,254
Axitinib and BSC utility source	AXIS patients	TA 333 historical estimates	£48,811	£83,829	£60,756
Axitinib and BSC utility source	AXIS patients	025 trial everolimus patients	£49,982	£83,829	£61,580
TRAE utility decrements	Exclude	Include	£42,414	£83,814	£56,445
Average patient weight	025 Western European patients	Ipsos UK estimate	£36,149	£73,145	£51,762

Abbreviations in table**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; NMA, network meta-analysis; OS, overall survival, TA, Technology Appraisal; TRAE, treatment-related adverse event.

The company carried out an additional scenario analysis at clarification stage as requested by the ERG, assuming a PFS and OS for axitinib equal to that of everolimus. The results of the scenario analysis, presented in Table 60, showed an increase of £4,799 per QALY in the ICER for nivolumab compared to axitinib. This resulted in an ICER of £47,215 per QALY gained.

Table 60. Scenario assuming PFS and OS for axitinib equal to everolimus

Treatment	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs)
				Costs	QALYs	Life years	
Nivolumab	£91,352.66	2.31	3.44				
Axitinib	£52,698.24	1.49	2.55	£38,654.42	0.82	0.89	£47,215.69
Everolimus	£38,920.38	1.69	2.55	£52,432.28	0.63	0.89	£83,829.24
BSC	£10,524.94	0.88	1.47	£80,827.72	1.43	1.97	£56,427.43
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

5.6.2.3 Probabilistic sensitivity analysis

The company performed a PSA to assess the joint parameter uncertainty around the base case results. The results across 10,000 iterations were presented in Section 5.8.1 and in Appendix 8 of the CS; details on the parameters and the distributions used were reported in Section 5.6.1 of the CS. All the parameters used in the model were varied except for intervention and comparator costs, and drug administration frequency.

The mean results of the PSA are presented in Table 61. The probabilistic ICER for nivolumab compared to everolimus was in line with the deterministic ICER, with a difference of £1,541 per QALY compared with the base case. The mean probabilistic ICERs for nivolumab compared to axitinib and nivolumab compared to BSC were greater by £5,511 and £3,650 per QALY, respectively.

The individual simulations from the PSA are shown in the scatter plots presented in Figure 51, Figure 52 and Figure 53 for nivolumab versus axitinib, everolimus and BSC, respectively. Upon visual inspection of the scatter plot, the probability of nivolumab being cost-effective compared to everolimus at a willingness-to-pay threshold of £50,000 per QALY seems low.

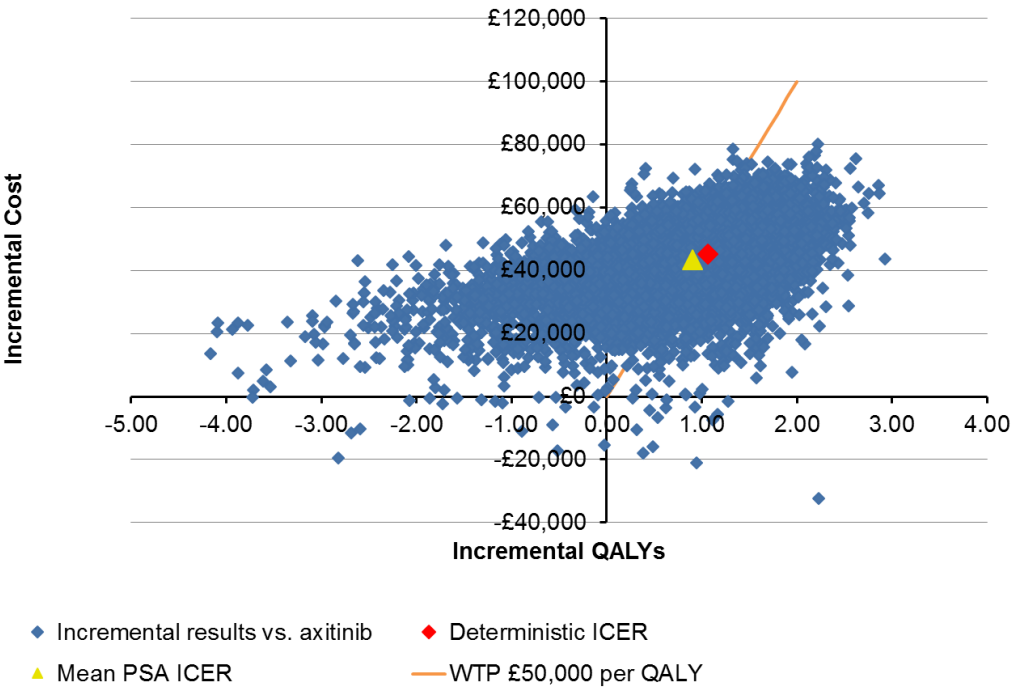
A proportion of the PSA simulations fell in the north-western quadrant when nivolumab was compared to axitinib or BSC, 11.8 % and 3.2% respectively. In these simulations, nivolumab was dominated by these two interventions. The PSA results for the comparison between nivolumab and axitinib, and nivolumab and BSC showed substantial uncertainty surrounding the cost-effectiveness results and in particular the QALY differentials, and a potentially non-linear relationship between incremental costs and QALYs. The ERG considers that these results are the reflection of the substantial uncertainty associated with the relative effectiveness, and in particular with the HRs estimated in the NMA.

Table 61. Mean results of probabilistic sensitivity analysis (adapted from CS, pg 204, Table 72)

Comparator	Costs	QALYs	LYG	Incremental, nivolumab versus comparator			ICER
				Costs	QALYs	LYG	
Nivolumab	£91,964	2.36	3.55				
Axitinib	£48,655	1.46	2.59	£43,310	0.90	0.96	£47,928
Everolimus	£39,127	1.72	2.62	£52,838	0.64	0.93	£82,288
BSC	£11,270	1.02	1.77	£80,694	1.34	1.78	£60,077

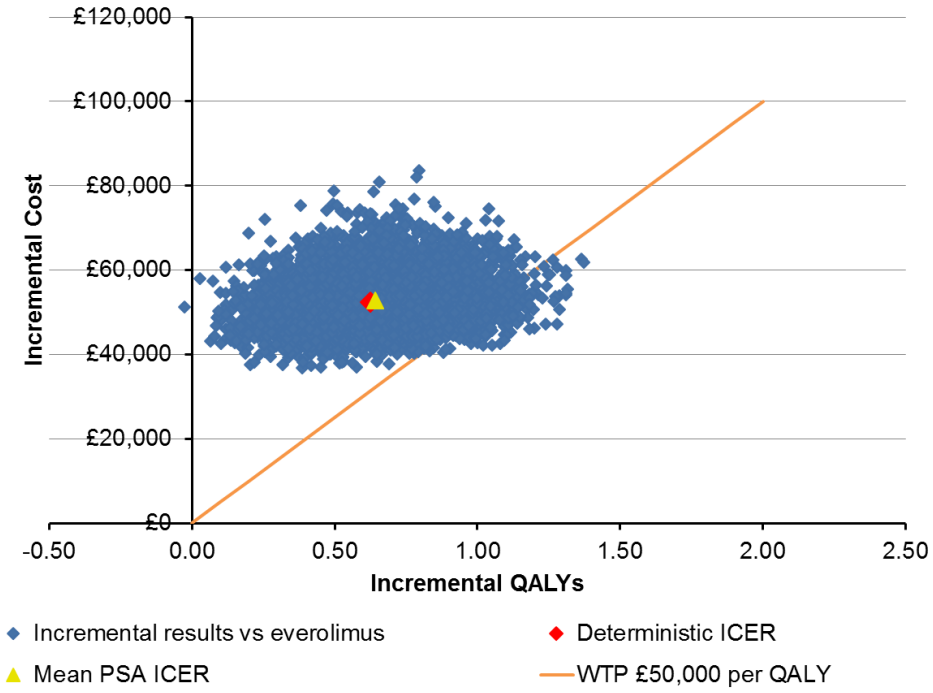
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life year(s) gained; QALY, quality-adjusted life year.

Figure 51. Distribution of cost-effectiveness simulation on the cost-effectiveness plane for nivolumab versus axitinib (CS, pg 203, Figure 50)



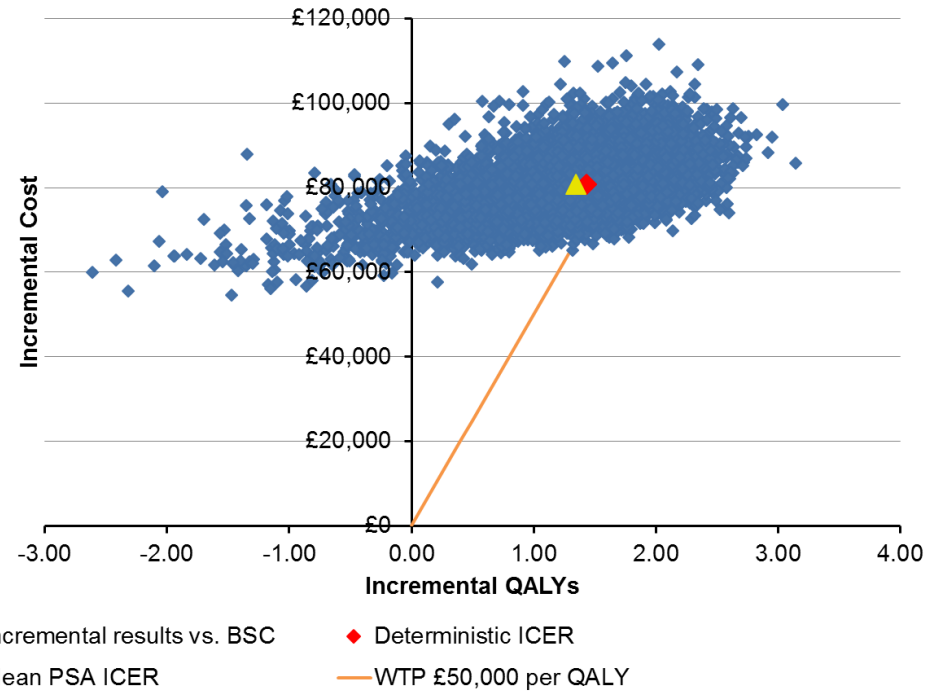
Abbreviations in figure: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 52. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for nivolumab versus everolimus (Appendix 8, pg 109, Figure 2)



Abbreviations in figure: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

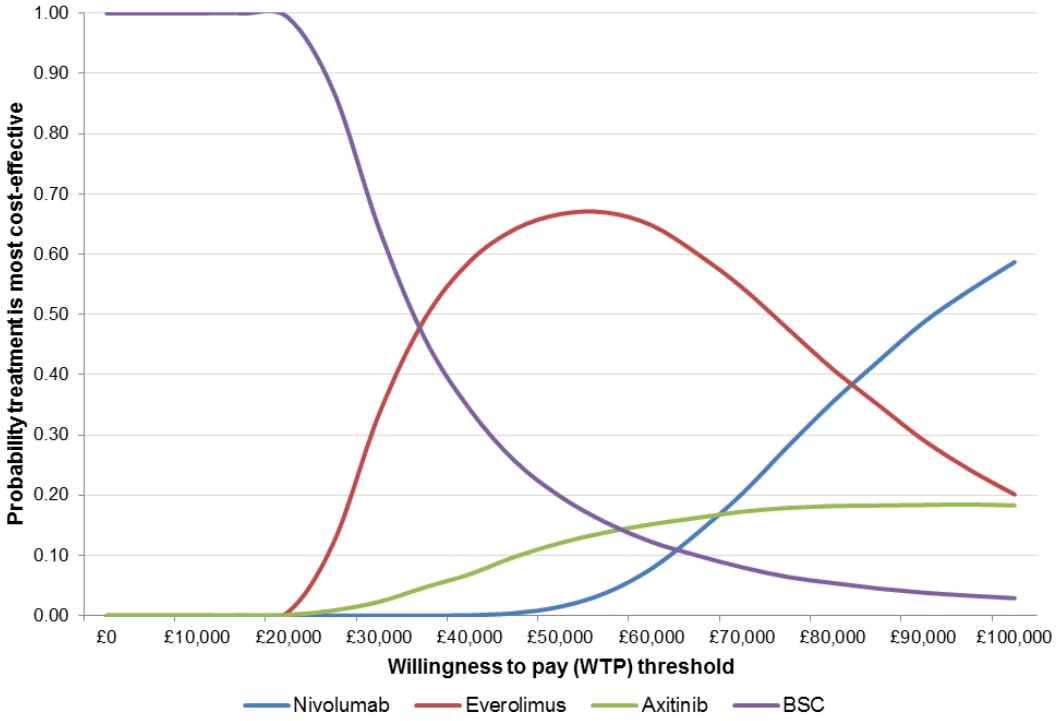
Figure 53. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for nivolumab versus BSC (Appendix 8, pg 109, Figure 3)



Abbreviations in figure: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

The company did not report cost-effectiveness acceptability curves (CEACs) for the pairwise or multiple comparisons in the CS, but included the CEACs for the multiple comparison in the electronic model, showed in Figure 54. BSC and everolimus were associated with the highest probability of being the most cost-effective option at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY, respectively. The probability of nivolumab being cost-effective at either threshold was null or close to zero. Nivolumab was estimated to have the highest probability of being the most cost-effective option for a WTP of £85,000 per QALY or higher; however, even at a threshold value of £100,000 per QALY the CEAC did not reach 0.60.

Figure 54. Cost-effectiveness acceptabilty curves



6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG identified several errors in the model, and implemented corrections to the company's model as detailed in Table 77. In particular, the ERG considers that the approach to the integration and joint modelling of overall survival (OS), progression-free survival (PFS) and time to discontinuation (TTD) was flawed, even though the impact of the errors found on the base-case model results was minor. These modelling issues, discussed in detail in Section 5.5.5, were:

- Not limiting the proportion of patients alive and progression-free (i.e. PFS health state) with the proportion of patients alive (i.e. OS), resulting in negative proportion of patients in health states. As the model implementation was slightly different depending on the intervention considered, i.e. nivolumab and everolimus or axitinib and best supportive care (BSC), the errors are assessed separately in Section 5.5.2.2. This issue had a very limited impact on the model results;

- Not limiting the proportion of patients on treatment (i.e. TTD) with the proportion of patients alive and/or alive and progression-free, resulting in the total number of patients in each state exceeding 100% of the patients at the beginning of the model. This modelling error had no impact on the base case results, but caused severe errors in alternative scenario, e.g. overestimating one of the incremental cost-effectiveness ratio (ICER) by £40,000 per quality-adjusted life year (QALY) in one of the scenarios considered by the ERG (i.e. using a generalised gamma model for TTD).

Additionally, the ERG identified three minor errors in the costs used in the model and reported in the company's submission (CS). The ERG obtained the correct costs from the sources cited and description provided in cases when HRG codes were reported. The correct administration cost for nivolumab is £185.53 and not £186.53 per administration, translating into £92.77 per week. The correct costs of CT scans and blood tests are £136.21 and £3.01, and not £136.00 and £3.00, respectively.

The results of the corrected model are presented in Table 62. Applying the corrections in the model led to an increase in the ICER compared to the company's base case by £692, £2,307 and £331 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively.

Table 62. Revised base case results

Treatment	Cost	LYs*	QALYs	Incremental costs Nivolumab versus	Incremental LYs Nivolumab versus	Incremental QALYs Nivolumab versus	ICER Nivolumab versus
Nivolumab	£91,325.93	3.39	2.30	-	-	-	-
Axitinib	£46,112.87	2.09	1.25	£45,213.06	1.30	1.04	**£43,109.08**
Everolimus	£38,932.79	2.55	1.69	£52,393.15	0.84	0.61	**£86,135.91**
BSC	£10,525.24	1.47	0.88	£80,800.69	1.92	1.42	**£57,096.08**

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

6.2 ERG scenario analysis

The ERG explores the impact of the uncertainty surrounding several modelling assumptions on the model results in scenario analyses, based on the company's revised base case. The scenarios explored were selected based on the ERG's critique of the CS in Section 5.5. The ERG looks at the impact of alternative assumptions on:

- Relative treatment effectiveness between axitinib and everolimus;
- Extrapolation of OS;
- Time to discontinuation TTD modelling choice;
- Health state utility values (HSUVs) associated to axitinib and BSC;
- Proportion of drug received for the estimation of drug acquisition costs;
- Subsequent therapy costs.

The results of the scenario analysis are reported in Table 63.

6.2.1 Relative treatment effectiveness between axitinib and everolimus

According to the company's and the ERG's clinical experts, axitinib is not inferior to everolimus in terms of comparative effectiveness profile. However, the results of the network meta-analysis (NMA) used to estimate the effectiveness of axitinib and BSC, as described in Section 5.5.5, showed everolimus to be superior to axitinib for both the OS and progression-free survival PFS. The ERG explores a scenario assuming equal effectiveness between axitinib and everolimus on the cost-effectiveness results.

It is worth noting that the opinion of the ERG's clinical experts was that axitinib would perform at least as well as everolimus. The ERG therefore considers that this scenario might provide an underestimation of the effectiveness of axitinib when compared to nivolumab.

6.2.2 Overall survival model

As discussed in Section 5.4.2.1, the company selected a generalised gamma model to extrapolate OS data from the trial, based on clinical expert feedback, even though the log-logistic model was the best fit to the data. The ERG explores a scenario analysis extrapolating OS using a log-logistic parametric model.

6.2.3 Time to discontinuation model

The company used spline-based models to fit and extrapolated TTD data collected from the CheckMate 025 trial. As discussed in Section 5.5.5.3, the ERG does not find the use of the spline-based model to be justified satisfactorily by the company. The ERG explores the impact on the results of using a simpler accelerated failure time (AFT) parametric model for TTD, given the presence of a substantial difference in the model estimates.

The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were not in agreement regarding the best relative fit to the data, as they indicated that the best-fitting distributions were the generalised gamma and log-normal models, respectively. The ERG tests both separately as part of the scenario analyses.

6.2.4 Health-state utility values

The HSUVs for axitinib and BSC during pre-progression are not considered appropriate by the ERG based on clinical expert opinion, as mentioned in Section 5.5.7. The ERG explores a scenario assuming the same HSUVs for axitinib and BSC as the ones used for everolimus and based on the CheckMate 025 trial.

6.2.5 Proportion of planned drug received

The company assumed that patients in the model receive a proportion of the planned doses of nivolumab and everolimus, based on the CheckMate 025 trial data, as discussed in Section 5.4.5.1 and Section 5.5.8.1. The ERG carries out two scenario analyses: the first including the cost of delayed doses for nivolumab, as opposed to excluding their cost as in the company's base case; the second assuming that patients received all the planned doses of both nivolumab and everolimus.

6.2.6 Subsequent therapy costs

The company assumed a one-off cost of subsequent therapy lines for patients who discontinued treatment, as discussed in Section 5.4.5.4 and Section 5.5.8.4. However, currently there are no

approved third-line treatment options for patients with advanced or metastatic renal cell carcinoma (RCC) in the UK. Furthermore, the ERG's clinical experts stated that there is no clinical benefit of administering treatment compared to BSC. The ERG explores a scenario analysis removing subsequent therapy costs from the model, assuming that patients would not receive further treatment after discontinuation.

Table 63. ERG's scenario analyses

	Results per patient	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
0	**Revised base case**							
	Total costs (£)	£91,325.93	£46,112.87	£38,932.79	£10,525.24	£45,213.06	£52,393.15	£80,800.69
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£43,109.08	£86,135.91	£57,096.08
1	**Efficacy estimates for axitinib equal to everolimus**							
	Total costs (£)	£91,325.93	£52,682.58	38,932.79	£10,525.24	£38,643.36	£52,393.15	£80.800.69
	QALYs	2.30	1.49	1.69	0.88	0.80	0.61	1.42
	ICER					£48,217.94	£86,135.91	£57,096.08
2	**Log-logistic model for OS**							
	Total costs (£)	£93,403.43	£47,376.86	£40,833.78	£10,977.50	£46,026.57	£52,569.65	£82,425.94
	QALYs	2.74	1.46	2.07	0.96	1.27	0.67	1.77
	ICER					£36,192.66	£78,873.78	£46,477.40
3	**Generalised gamma (dependent) model for TTD**							
	Total costs (£)	£94,929.80	£46,112.87	£42,399.10	£10,525.24	£48,816.93	£52,530.70	£84,404.56
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£46,545.24	£86,362.05	£59,642.68
4	**Log-normal (dependent) model for TTD**							
	Total costs (£)	£90,791.00	£46,112.87	£40,658.59	£10,525.24	£44,678.13	£50,132.41	£80,265.77
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£42,599.04	£82,419.19	£56,718.09
5	**Health-state utility values for axitinib and BSC equal to everolimus arm of CheckMate 025**							
	Total costs (£)	£91,325.93	£46,112.87	£38,932.79	£10,525.24	£45,213.06	£52,393.15	£80,800.69
	QALYs	2.30	1.41	1.69	1.00	0.89	0.61	1.30

	Results per patient	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
	ICER					£50,946.22	£86,135.91	£62,378.68
6	**Include delayed doses of nivolumab for drug-related costs calculation**							
	Total costs (£)	£94,973.35	£46,112.87	£38,932.79	£10,525.24	£48,860.48	£56,040.57	£84,448.12
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£46,586.77	£92,132.38	£59,673.45
7	**Assuming patients receive all planned doses of nivolumab and everolimus**							
	Total costs (£)	£96,873.77	£46,137.97	£40,071.72	£10,525.24	£50,735.80	£56,802.05	£86,348.53
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£48,374.82	£93,384.28	£61,016.34
8	**Removing subsequent therapy costs**							
	Total costs (£)	£85,189.23	£38,205.19	£30,797.95	£10,525.24	£46,984.04	£54,391.28	£74,663.99
	QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
	ICER					£44,797.65	£89,420.90	£52,759.71

Abbreviations used in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year; TTD, time-to-discontinuation.

6.3 ERG base case ICER

In this Section the ERG presents the model results using its preferred modelling approaches and assumptions, as discussed and explored throughout the report. The ERG's base case included changes in the following assumptions:

1. Assuming equal efficacy of axitinib and everolimus for both PFS and OS, in line with clinical expert opinion;

2. Using a log-normal model for TTD. The ERG notes that a generalised gamma model would fit the data equally well and produce different results;

3. Assuming patients would receive the entire planned doses of nivolumab and everolimus. The proportion of axitinib received by patients is assumed equal to 102% as in the company's model, according to clinical expert opinion sought by the ERG;

4. Assuming the same HSUVs for axitinib and BSC as the values set for everolimus and estimated from the CheckMate 025 trial, in line with clinical expert opinion;

5. Removing the cost of subsequent therapies, as there are no further lines of treatment currently reimbursed by the National Health Service (NHS).

The ERG's base case ICER is presented in Table 64. The cost-effectiveness efficiency plane, showing the simultaneous comparison between the treatment alternatives, is included in Figure 55. The results show that nivolumab is the most expensive alternative by at least £45,000 per patient on average compared to the most expensive of the comparators (i.e. axitinib). Nivolumab is expected to increase the average QALYs per patient by 0.61 compared to axitinib or everolimus in the ERG's base case. However, the ERG notes that the comparison to axitinib is based on a conservative estimate of the effectiveness of axitinib, and that based on clinical opinion sought by the ERG the differential effectiveness may be overestimated in this scenario. The results should therefore be interpreted carefully in the light of the assumption that axitinib is at least as effective as everolimus: any additional benefit in terms of QALYs accrued would increase the ICER for the comparison between nivolumab and axitinib.

The ERG presents an alternative scenario using a generalised gamma model for TTD, considered equally as plausible as the base case in which a log-normal curve is selected, based on the relative measures of goodness of fit to the data associated to the two curves. The results are shown in Table 66. All the pairwise ICERs in the alternative scenario resulted to increase, due to the longer time on treatment associated with nivolumab.

Table 64. ERG's base case ICER

Results per patient	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Revised base case							
Total costs (£)	£91,325.93	£46,112.87	£38,932.79	£10,525.24	£45,213.06	£52,393.15	£80,800.69
QALYs	2.30	1.25	1.69	0.88	1.05	0.61	1.42
ICER					**£43,109.08**	**£86,135.91**	**£57,096.08**
Efficacy estimates for axitinib equal to everolimus							
Total costs (£)	£91,325.93	£52,682.58	£38,932.79	£10,525.24	£38,643.36	£52,393.15	£80.800.69
QALYs	2.30	1.49	1.69	0.88	0.80	0.61	1.42
ICER (compared with base case)					£48,217.94	£86,135.91	£57,096.08
ICER (with all changes incorporated)					**£48,217.94**	**£86,135.91**	**£57,096.08**
Log-normal (dependent) TTD model							
Total costs (£)	£90,791.00	£52,682.58	£40,658.59	£10,525.24	£38,108.43	£50,132.41	£80,265.77
QALYs	2.30	1.49	1.69	0.88	0.80	0.61	1.42
ICER (compared with base case)					£42,599.04	£82,419.19	£56,718.09
ICER (with all changes incorporated)					**£47,550.47**	**£82,419.19**	**£56,718.09**
Assuming patients receive all planned doses of nivolumab and everolimus							
Total costs (£)	£96,292.06	£52,707.41	£41,916.93	£10,525.24	£43,584.65	£54,375.13	£85,766.82
QALYs	2.30	1.49	1.69	0.88	0.80	0.61	1.42
ICER (compared with base case)					£48,374.82	£93,384.28	£61,016.34
ICER (with all changes incorporated)					**£54,383.53**	**£89,394.35**	**£60,605.29**
Health-state utility values for axitinib and BSC equal to everolimus arm of CheckMate 025							
Total costs (£)	£96,292.06	£52,707.41	£41,916.93	£10,525,24	£43,584.65	£54,375.13	£85,766.82
QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
ICER (compared with base case)					£50,946.22	£86,135.91	£62,378.68

Results per patient	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
ICER (with all changes incorporated)					**£71,654.48**	**£89,394.35**	**£66,212.57**
Removing subsequent therapy costs							
Total costs (£)	£89.950.79	£44,859.06	£33,997.18	£10,525.24	£45,091.73	£55,953.61	£79,425.55
QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
ICER (compared with base case)					£44,797.65	£89,420.90	£52,759.71
ICER (with all changes incorporated)					£74,132.16	£91,989.42	£61,317.07
ERG preferred base case ICER					**£74,132.16**	**£91,989.42**	**£61,317.07**

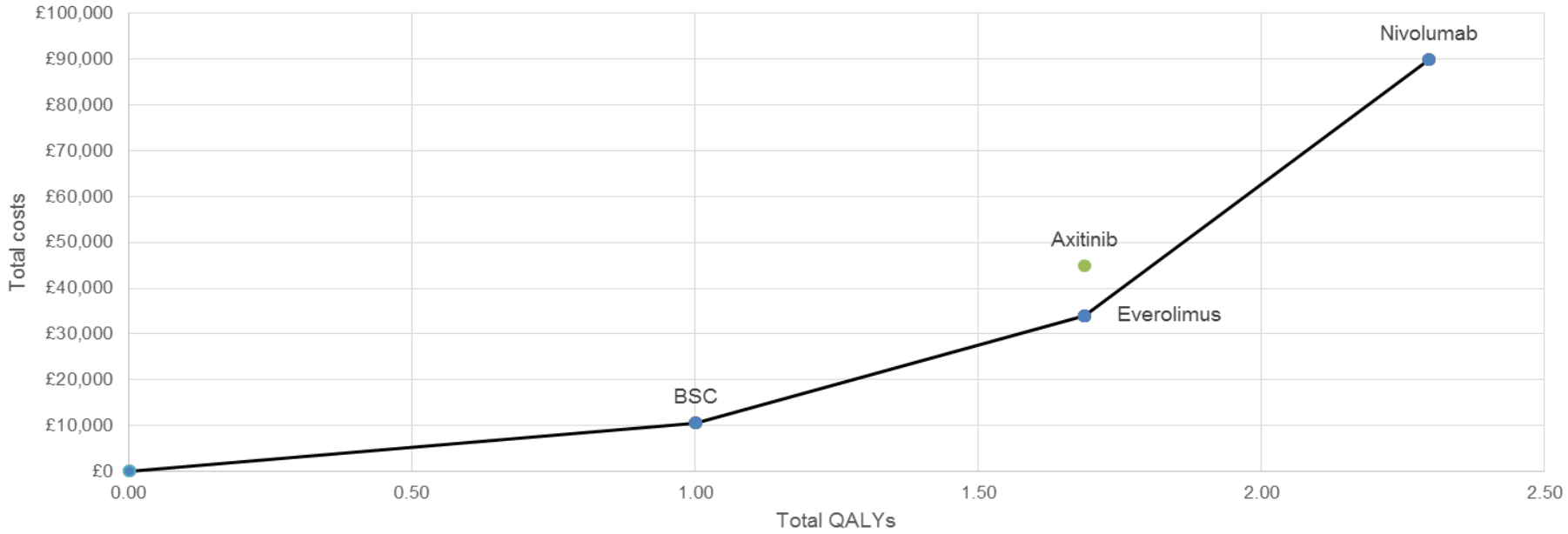
Abbreviations used in table: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year; TTD, time to discontinuation.

Table 65. ERG's base case incremental analysis

Comparator	Costs	QALYs	Incremental measures*		
			Costs	QALYs	ICER
BSC	£10,525.24	1.00	-	-	-
Everolimus	£33,997.18	1.69	£23,471.94	0.69	£34,162.67
Axitinib	£44,859.06	1.69	£10,861.88	0.00	Absolutely dominated
Nivolumab	£89,950.79	2.30	£55,953.61	0.61	£91,989.42

Abbreviations used in table: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year.
Note: *, compared to the less expensive most efficient comparator.

Figure 55. Cost-effectiveness efficiency frontier, ERG's base case scenario



Abbreviation in figure: BSC, best supportive care; QALY, quality-adjusted life year.

Table 66. Alternative scenario using a generalised gamma model for TTD

Results per patient	Nivolumab (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
ERG's alternative scenario using a generalised gamma model for TTD							
Total costs (£)	£94,551.72	£44,859.06	£36,093.57	£10,525.24	£49,629.67	£58,458.16	£84,026.49
QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
ICER (with all changes incorporated)					**£81,696.24**	**£96,106.97**	**£64,869.02**
Abbreviations used in table: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year; TTD, time to discontinuation.							

7 END OF LIFE

The company reports (CS, pg 131, Table 27, Section 4.13) the median life expectancy is less than 12 months with BSC, and less than 24 months with established standard care. Based on data from CheckMate 025, nivolumab may offer extension to life of at least 5 months, based on the median survival time of 25 months with nivolumab versus the current NHS treatment of ≤20 months (19.6 months with everolimus). No data of mean survival time were presented in the CS.

The ERG is uncertain if the additional mean survival for nivolumab over axitinib would meet the end of life criteria.

8 OVERALL CONCLUSIONS

The company presented evidence from a head-to-head trial (CheckMate 025) of nivolumab versus everolimus in pre-treated patients with advanced/metastatic RCC. CheckMate 025 is a well-conducted trial, and it is reflective of English clinical practice. In addition, safety and clinical efficacy results of CheckMate 025 are relevant to the decision problem as outlined in the NICE final scope for this STA.

Axitinib is the only recommended treatment for second-line advanced/metastatic RCC by NICE in England. However, there are no direct RCT data comparing nivolumab with axitinib. Nivolumab was therefore compared with axitinib through a network meta-analysis (NMA) involving trials with potentially dissimilar baseline characteristics in terms of prior treatment (e.g. cytokines and/or VEGF-targeted therapy, etc.), number of prior treatments, prognostic risk scores, differences in maturity of the survival data, and differences in whether or not crossover had occurred (and if so, whether it had been adjusted appropriately).

The company presented an economic analysis comparing nivolumab to axitinib, everolimus and best supportive care (BSC) for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC). The economic analysis and underlying assumptions were clearly reported and presented. The electronic model was flexible and transparent. The company used advanced statistical methods in cases where standard methods were not considered sufficient.

The ERG considers the evidence submitted by the company sufficient to inform the decision problem. The treatment effectiveness estimates used in the model for nivolumab and everolimus were based on data from the phase III trial CheckMate 025[37]. In the absence of head-to-head trial data for nivolumab compared to axitinib and to placebo (to estimate the effectiveness of BSC), an NMA was carried out to estimate the relative effectiveness between treatments. The resulting hazard ratios (HRs) were used to estimate and extrapolate the clinical outcomes. However, the company's and the ERG's clinical experts did not consider the results of the NMA as clinically plausible, as they showed everolimus to be superior to axitinib.

The company reported incremental cost-effectiveness ratios (ICERs) of £42,417, £83,829 and £56,427 per QALY for the pairwise analysis of nivolumab compared to axitinib, everolimus and BSC, respectively. According to the company's probabilistic sensitivity analysis (PSA), BSC and everolimus were associated with the highest probability of being the most cost-effective option at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per quality-adjusted life year (QALY), respectively. The probability of nivolumab being cost-effective in correspondence of both afore-mentioned thresholds threshold was null or close to zero. The company estimated that nivolumab was expected to have the highest probability of being the most cost-effective option among the considered alternatives for a WTP of £85,000 per QALY or higher. However, even at a threshold value of

£100,000 per QALY the cost-effectiveness acceptability curve (CEAC) did not reach 0.60 in the company's analysis.

The ERG identified errors in the way treatment effectiveness was incorporated in the model and how the three components determining the model state, i.e. overall survival, progression-free survival and time-to-discontinuation, were integrated. When the ERG corrected these errors, in addition to a few minor discrepancies in the cost data, the ICERs were £43,109, £86,136 and £57,096 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively. These ICERs are higher than the company's base case by £692, £2,307 and £331 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively.

The ERG carried out an additional analysis based on its preferred modelling approaches and assumptions. The ERG's base case was based on the following assumptions:

- Equal effectiveness profile (i.e. overall survival and progression-free survival) between axitinib and everolimus. This is because, according to clinical expert opinion, axitinib is considered at least equally as effective as everolimus. According to the clinical experts consulted by the ERG, the assumption of equal effectiveness between everolimus and axitinib might result in overestimating the relative benefits of nivolumab compared to axitinib;

- Equal health-related quality of life (HRQoL) profile between axitinib, BSC and everolimus. The clinical expert interviewed by the ERG disagreed with the company's assumption of a lower HRQoL associated to patients treated with axitinib in both pre- and post-progression compared to everolimus;

- Using a log-normal distribution for time-to-discontinuation instead of the spline-based model proposed by the company. The ERG considers the company's justification not sufficient and prefers using a simpler model which demonstrated to fit well the data;

- Assuming that patients receive all planned doses of everolimus and nivolumab. The ERG considers that the calculations for the planned doses received were not sufficiently clear, and that the company did not justify the assumption of a constant reduction in the quantity of drug used over time;

- No subsequent therapy costs, as currently there are no approved and reimbursed third-line treatment options for advanced or metastatic RCC in the UK.

The ERG's base case ICERs were £74,132, £91,989 and £61,317 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively. The ERG also explored an equally plausible scenario

by varying the distribution used to model TTD; the ICERs using a generalised gamma model were £81,696, 96,107 and £64,869 per QALY for nivolumab compared to axitinib, everolimus and BSC, respectively.

The ERG highlights substantial uncertainty on the relative treatment effectiveness between everolimus and axitinib, and, by propagation, between nivolumab and axitinib. In particular, the ERG notes that the company did not analyse appropriately the adjustments made to the relative treatment effects because of the presence of treatment switching in the trials included in the NMA. The ERG warns that the evidence presented is not considered sufficient to inform an analysis of the comparative effectiveness and cost-effectiveness profiles of everolimus and axitinib. The results for these two alternatives should be compared with caution, as they are associated with a substantial degree of unaccounted uncertainty.

The ERG assumed equal effectiveness between everolimus and axitinib based on clinical opinion, as the base case estimates presented by the company were deemed implausible. As the clinical experts stated that axitinib would be at least as effective as everolimus, the ERG's base case results are likely to underestimate the effectiveness associated to axitinib. In conclusion, based on the assumptions made in the model and according to clinical expert opinion, the ICER for the comparison between nivolumab and axitinib might have been underestimated.

8.1 Implications for research

Currently in England, axitinib is the only recommended treatment in patients with advanced/metastatic RCC who have had prior treatment. Until November 2015, everolimus was also available through the CDF in patients who have had prior treatment with only one TKI and are contraindicated to second-line axitinib therapy or show excessive toxicity to axitinib within three months of treatment initiation and have no evidence of disease progression. The only direct evidence for nivolumab compared to the treatments identified in the NICE final scope is with everolimus (CheckMate 025). Therefore, robust direct evidence of nivolumab compared with axitinib are needed in the treatment of patients with advanced/metastatic RCC who have received previous treatment.

The ERG notes that the source of uncertainty considered most influential on the results is associated to the relative effectiveness between axitinib and nivolumab, originating from the uncertainty on the comparative effectiveness between axitinib and everolimus. A robust analysis of the comparative treatment effectiveness should be carried out, accounting appropriately for the methodologies used in the trials (e.g. crossover adjustments) and potential differences in the patient populations. An economic analysis including all treatment options, such as in the context of a multiple technology assessment (MTA), should be performed once robust relative treatment effectiveness estimates are obtained.

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10 APPENDICES

10.1 Quality assessment

Table 67. Quality assessment of CheckMate 010 (adapted from CS, Section 4.11, pg 78)

Study question	**How is the question addressed in the study?**	
	Company	**ERG**
Were attempts made to minimise selection bias?	Yes. Patients randomly assigned to a dose cohort and randomisation stratified by MSKCC risk group and number of prior regimens.	Yes, randomisation was stratified by MSKCC risk group, and number of prior treatment regimens in the metastatic setting.
Do the selected patients represent the eligible population for the intervention?	Yes. Adult patients with advanced RCC with a clear-cell component who had received prior treatment with at least one anti-angiogenic therapy enrolled.	Yes, eligible patients had RCC with a clear-cell component and had received at least one prior treatment with anti-angiogenic therapy.
Did the setting reflect UK practice?	Yes. Baseline demographics and disease characteristics representative of typical pre-treated patients with advanced RCC in UK clinical practice. Nivolumab administered by IV in the hospital setting as would be the case in UK practice. Dose range of 0.1-10mg/kg crosses that for which marketing authorisation is anticipated (3mg/kg).	Yes, study population is a reflective of UK clinical practice post first-line therapy. In addition, nivolumab was given via IV in the hospital setting.
Were all participants accounted for at study conclusion?	Yes.	Yes, study flow diagram depicts number of patients randomised, number completed, and number withdrawn/discontinued and with reasons
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes. Efficacy assessed in terms of PFS, OS and ORR. These are clinically relevant outcomes named in the decision problem. Response was assessed according to conventional RECIST criteria, and survival curves were estimated according to the KM method. These are well-established and validated methods of assessment.	Yes, primary outcome measure was PFS, and secondary outcomes included ORR, OS and AEs. Tumour response was based on RECIST criteria, median OS was estimated using Kaplan-Meier methodology.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Primary efficacy analysis was performed according to the intention-to-treat principle with standard censoring methods used to account for missing data.	Yes, efficacy analysis was based on all randomised patients.
Are the study results internally valid?	Yes. Analyses conducted in accordance with approved statistical	Yes

Study question	How is the question addressed in the study?	
	Company	**ERG**
	methods.	
Are the findings externally valid?	Yes. Clinical analyses of direct relevance to the decision problem and reflective of evidence on which treatment decisions will be made in clinical practice.	Yes, nivolumab demonstrated anti-tumour activity across the 3 doses, and with a manageable safety profile

Abbreviations used in table: IV, intravenous; KM, Kaplan-Meier; MSKCC, Memorial Sloane Kettering Cancer Centre; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 68. Quality assessment of CheckMate 003 (adapted from CS, Section 4.11, pg 79)

Study question	How is the question addressed in the study?	
	Company	**ERG**
Were attempts made to minimise selection bias?	Yes. Patients allocated sequentially during cohort enrolment.	Yes, patients were treated with nivolumab 10 mg/kg in an initial expansion cohort, followed by subsequent expansion cohort at 1 mg/kg.
Do the selected patients represent the eligible population for the intervention?	Yes. Adult patients with treatment-refractory solid tumours including advanced RCC patients enrolled.	Yes, patient population had been previously treated with anti-angiogenic therapy for solid tumours including advanced RCC
Did the setting reflect UK practice?	Yes. Baseline demographics and disease characteristics representative of typical pre-treated patients with advanced RCC in UK clinical practice. Nivolumab administered by IV in the hospital setting as would be the case in UK practice. Dose range of 0.1-10mg/kg crosses that for which marketing authorisation is anticipated (3mg/kg).	Yes, baseline clinical and demographic characteristics are a representative of UK clinical practice. Nivolumab was given via IV in an outpatient clinic setting at a dose of 1 or 10 mg/kg once every two weeks.
Were all participants accounted for at study conclusion?	Yes.	Yes.
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes. Efficacy assessed in terms of PFS, OS and ORR. These are clinically relevant outcomes named in the decision problem. Response was assessed according to conventional RECIST criteria and survival curves were estimated according to the KM	Yes, efficacy outcomes included ORR (per RECIST), OS, PFS, and duration of response. Survival (OS, PFS) curves were estimated using KM methodology.

Study question	How is the question addressed in the study?	
	Company	**ERG**
	method. These are well-established and validated methods of assessment.	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Primary efficacy analysis was performed according to the intention-to-treat principle, with standard censoring methods used to account for missing data.	Unclear, no information provided in the publication.
Are the study results internally valid?	Yes. Analyses conducted in accordance with approved statistical methods.	Yes, statistical analyses were based on approved and valid methods.
Are the findings externally valid?	Yes. Clinical analyses of direct relevance to the decision problem and reflective of evidence on which treatment decisions will be made in clinical practice.	Yes, the results are of relevance to the decision problem, i.e. nivolumab demonstrated durable responses that persisted in some responders after drug discontinuation.

Abbreviations used in table: IV, intravenous; KM, Kaplan-Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 69. Quality assessment of trials included in the NMA (adapted from CS, pg 99-102, Table 12, Appendix 2)

Study name	Jadad score	ACG	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
AXIS	3	A	Unclear; the randomisation was carried out appropriately by independent randomisation group using a permuted block design of size within each stratum	Low risk; the concealment of treatment allocation was adequate	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; this was an open-label study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00678392)	Low risk; the safety and efficacy analysis was done using mITT/ITT population
GOLD	3	A	Low risk; the randomisation list for the patients was produced by the	Low risk; the concealment of treatment allocation was	Low risk; there was no significant difference in the baseline	High risk; this was an open-label	Low risk; the withdrawals, completers, and the specific	Low risk; author has measured all the outcomes that have been reported in	Low risk; the safety was done using mITT, and

Study name	Jadad score	ACG	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
			provider of the interactive web-based and voice response system using a validated system that automated the random assignment of patient numbers to randomisation numbers	adequate via interactive web-based and voice response system	characteristics reported between the two treatment arms	study	reasons for withdrawal were reported	published protocol and in clinical trial registry (NCT01223027)	the efficacy analysis was done using ITT population
INTORSECT	3	A	Low risk; the randomisation was carried out appropriately via a computerised, centrally located randomisation system	Low risk; the concealment of treatment allocation was adequate via a computerised, centrally located randomisation system	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; this was an open-label study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00474786).	Low risk; the safety and efficacy analysis was done using mITT/ITT population
RECORD-1	5	A	Low risk; the randomisation was carried out appropriately, centrally via validated computer system	Low risk; the concealment of treatment allocation was adequate via a centrally, interactive voice response system	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	Low risk; this was a double-blind study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00410124)	Low risk; the safety and efficacy analysis was done using ITT/mITT population
RECORD-3	2	B	Not clear; this was a randomised trial but the method of randomisation was not reported	Not clear; the method of concealment of treatment allocation was not reported	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; this was an open-label study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Not clear; there was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; the safety analysis was done using mITT, and the efficacy analysis was done using ITT population

Study name	Jadad score	ACG	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
TARGET	3	B	Not clear; this was a randomised trial but the method of randomisation was not reported	Not clear; the method of concealment of treatment allocation was not reported	Low risk; baseline characteristics were well balanced between the two arms	Low risk; this was a double-blind study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00073307)	Low risk; the safety and efficacy analysis was done using mITT/ITT population
TIVO-1	2	B	Not clear; this was a randomised trial but the method of randomisation was not reported	Not clear; the method of concealment of treatment allocation was not reported	Low risk; baseline characteristics were well balanced between the two arms	High risk; this was an open-label study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01030783)	Low risk; the safety analysis was done using mITT, and the efficacy analysis was done using ITT population
VEG105192	4	B	Low risk; randomisation codes were generated using central randomisation method	Not clear; the method of concealment of treatment allocation was not reported	Low risk; there was no significant difference in the baseline characteristics reported between the two treatment arms	Low risk; this was a double-blind study	Low risk; the withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00334282)	Low risk; the safety and efficacy analysis was done using ITT population
Yang 2003	2	B	Not clear; this was a randomised trial but the method of randomisation was not reported	Not clear; the method of concealment of treatment allocation was not reported	Low risk; there was no significant difference in the baseline characteristics reported between the treatment arms	Low risk; this was a double-blind study	Not clear; withdrawals and reasons for withdrawals were not reported	Not clear; there was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; the safety and efficacy analysis was done using ITT population

Abbreviations used in table: ACG, allocation concealment grade; ITT, intention-to-treat; mITT, modified intention-to-treat; NMA, network meta-analysis; RCT, randomised controlled trial.

10.2 Participant flow

Figure 56. Study flow diagram of CheckMate 025 (reproduced from CS, pg 64, Figure 7)

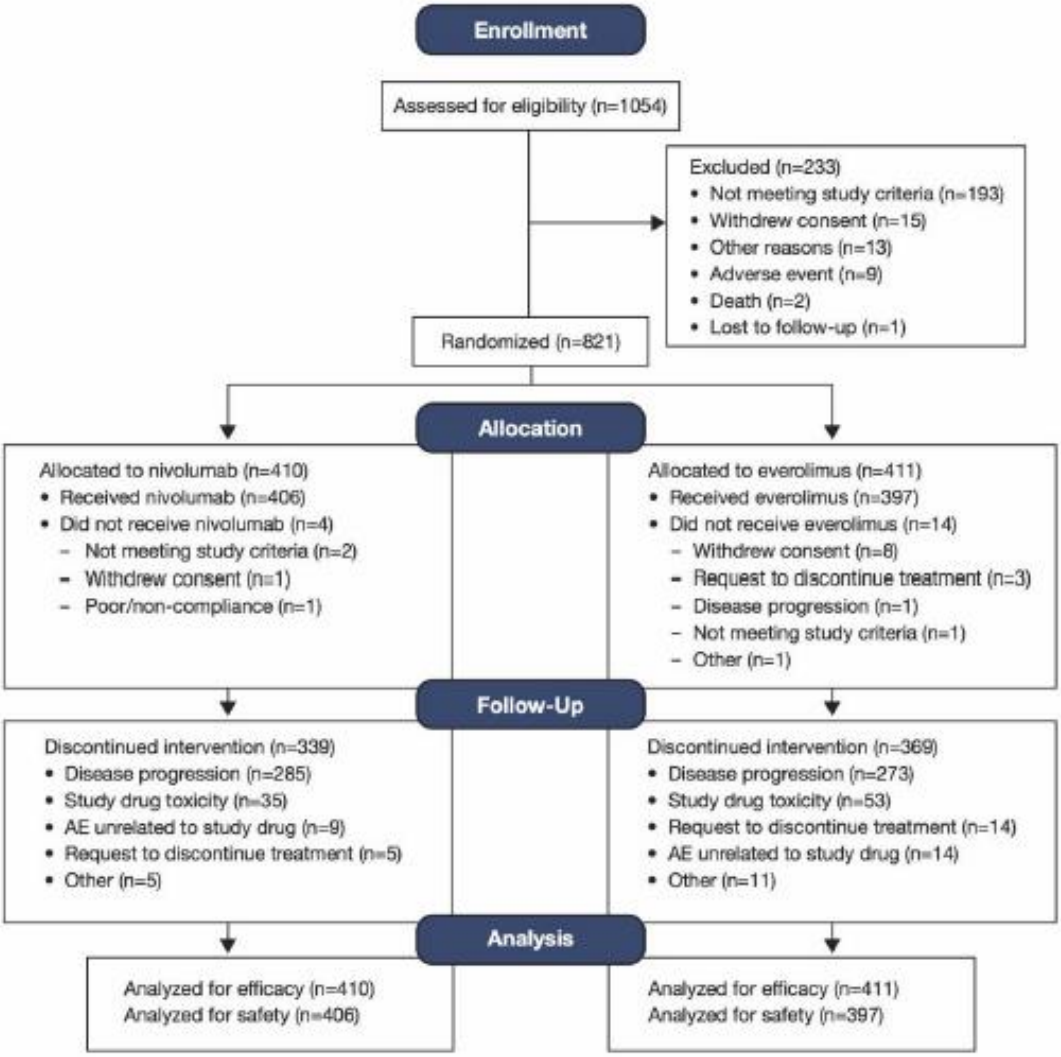
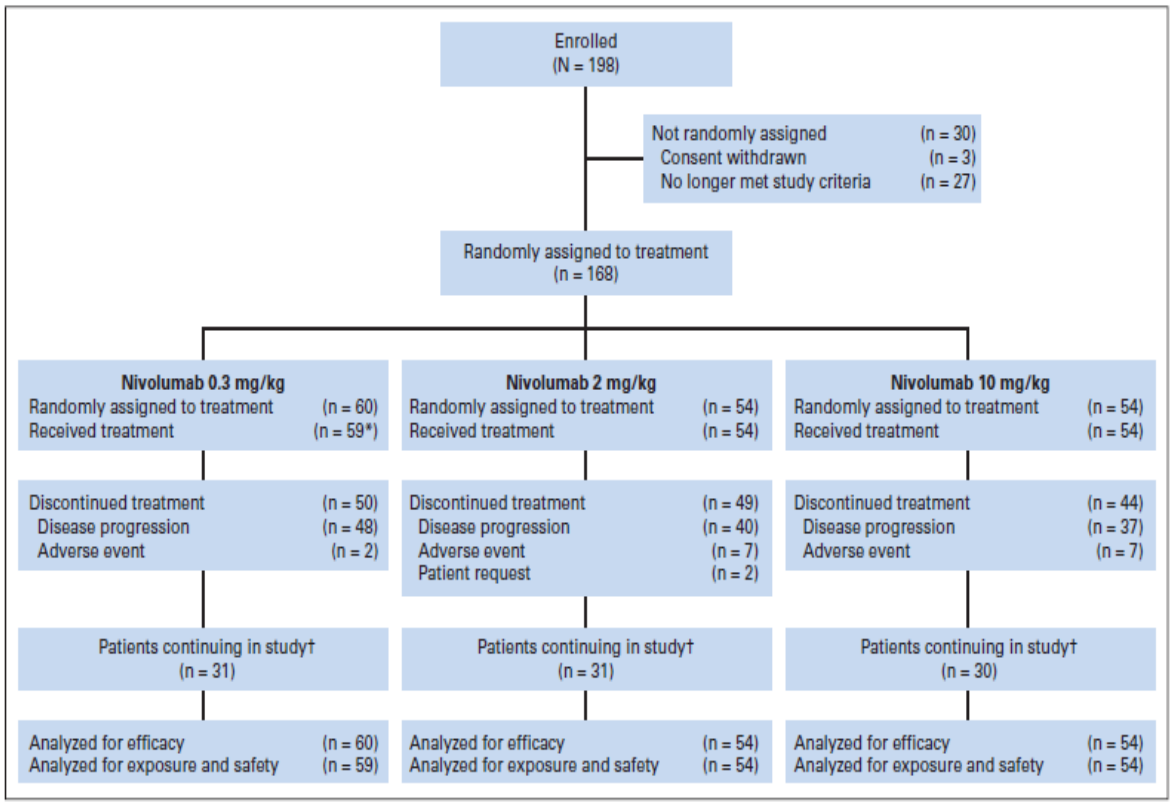


Figure 57. Study flow diagram of CheckMate 010



Source: Motzer et al 2015[65]

10.3 Baseline characteristics

Table 70. Characteristics of participants in AXIS, GOLD and INTORSECT (reproduced from CS, Appendix 5, pg 94-5, Table 10, Section 4.10)

	AXIS		**GOLD**		**INTORSECT**	
Baseline characteristic	Axitinib (n=361)	Sorafenib (n=362)	Dovitinib (n=284)	Sorafenib (n=286)	**Temsirolimus (n=259)**	**Sorafenib (n=253)**
Age, median years (range)	61 (20-82)	61 (22-80)	61 (29-89)	61 (18-81)	60 (19-82)	61 (21-80)
Gender, male n (%)	265 (73)	258 (71)	213 (75)	219 (77)	193 (75)	192 (76)
Race, Caucasian n (%)	278 (77)	269 (74)	233 (82)	232 (81)	178 (69)	163 (64)
MSKCC risk group, n (%)	Favourable: 100 (28) Intermediate: 134 (37) Poor: 118 (33) NA: 9 (2)	Favourable: 101 (28) Intermediate: 130 (36) Poor: 120 (33) NA: 11 (3)	Favourable: 50 (20) Intermediate: 164 (58) Poor: 62 (22)	Favourable: 59 (21) Intermediate: 162 (57) Poor: 65 (23)	Favourable: 50 (19) Intermediate: 178 (69) Poor: 31 (12)	Favourable: 44 (17) Intermediate: 177 (70) Poor: 32 (13)
IMDC risk group, n (%)	Favourable: 66 (18) Intermediate: 236 (65) Poor: 37 (10) NA: 22 (6)	Favourable: 79 (22) Intermediate: 225 (62) Poor: 34 (9) NA: 24 (7)	-	-	-	-
Karnofsky PS, n (%)	-	-	100: 83 (29) 90: 93 (33) 80: 73 (26) 70: 35 (12)	100: 73 (26) 90: 101 (35) 80: 83 (29) 70: 20 (10)	-	-
Common metastasis site, n (%)	-	-	Lung: 224 (79) Lymph nodes: 144 (51) Bone: 99 (35) Liver: 94 (33)	Lung: 216 (76) Lymph nodes: 147 (51) Bone: 119 (42) Liver: 94 (33)	-	-
Previous nephrectomy, n (%)	-	-	272 (96)	260 (91)	223 (86)	219 (87)
Time from initial diagnosis to randomisation, median months (range)	-	-	-	-	-	-
Previous anti-	Sunitinib: 194 (54)	Sunitinib: 195 (54)	Sunitinib: 260 (92)	Sunitinib: 253 (88)	-	-

	AXIS		GOLD		INTORSECT	
angiogenic therapy, n (%)	Cytokines: 126 (35) Bevacizumab: 29 (8)	Cytokines: 125 (35) Bevacizumab: 30 (8)	Bevacizumab: 10 (4) Axitinib: 3 (1) Pazopanib: 10 (4) Other: 1 (<1)	Bevacizumab: 11 (4) Axitinib: 6 (2) Pazopanib: 11 (4) Other: 5 (2)		
Abbreviations in table: IMDC, International Metastatic Renal Cell Carcinoma Database; MSKCC, Memorial Sloan Kettering Cancer Centre; PS, performance status.						

Table 71. Characteristics of participants in RECORD-1, RECORD-3 and TARGET (reproduced from CS, Appendix 5, pg 96-7, Table 11, Section 4.10)

	RECORD-1		RECORD-3[a]		TARGET	
Baseline characteristic	Everolimus plus BSC (n=277)	Placebo plus BSC (n=139)	Everolimus (n=99)	Sunitinib (n=108)	Sorafenib (n=451)	Placebo (n=452)
Age, median years (range)	61 (27-85)	60 (29-79)	61 (29-82)	62 (20-89)	58 (19-86)	59 (29-84)
Gender, male n (%)	216 (78)	106 (76)	74 (75)	80 (74)	315 (70)	340 (75)
Race, Caucasian n (%)	-	-	74 (75)	70 (65)	-	-
MSKCC risk group, n (%)	Favourable: 81 (29) Intermediate: 156 (56) Poor: 40 (14)	Favourable: 39 (28) Intermediate: 79 (57) Poor: 21 (15)	Favourable: 21 (21) Intermediate: 65 (66) Poor: 13 (13)	Favourable: 36 (33) Intermediate: 64 (59) Poor: 8 (7)	Intermediate: 218 (48) Low: 233 (52) Missing: 0	Intermediate: 223 (49) Low: 228 (50) Missing: 1 (<1)
IMDC risk group, n (%)	-	-	-	-	-	-
Karnofsky PS, n (%)	100: 78 (28) 90: 98 (35) 80: 72 (26) 70: 28 (10) Missing: 1 (<1)	100: 41 (30) 90: 53 (38) 80: 30 (22) 70: 15 (11) Missing: 0	≥90: 77 (78) 80: 19 (19) 70: 3 (3)	≥90: 79 (73) 80: 22 (20) 70: 7 (7)	-	-
Common metastasis site, n (%)	Lymph nodes: 210 (76) Lung: 203 (73) Bone: 103 (37) Liver: 92 (33) Other: 140 (51)	Lymph nodes: 97 (70) Lung: 112 (81) Bone: 42 (30) Liver: 53 (38) Other: 59 (42) Kidney: 20 (14)	Lung: 66 (67) Bone: 23 (23) Lymph node: 17 (17) Liver: 14 (14)	Lung: 76 (70) Bone: 27 (25) Lymph node: 12 (11) Liver: 15 (14)	Lung: 348 (77) Liver: 116 (26)	Lung: 348 (77) Liver: 117 (26)

	RECORD-1		RECORD-3[a]		TARGET	
Baseline characteristic	Everolimus plus BSC (n=277)	Placebo plus BSC (n=139)	Everolimus (n=99)	Sunitinib (n=108)	Sorafenib (n=451)	Placebo (n=452)
	Kidney: 34 (12) Brain: 17 (6)	Brain: 12 (9)				
Previous nephrectomy, n (%)	269 (97)	133 (96)	-	-	422 (94)	421 (93)
Time from initial diagnosis to randomisation, median months (range)	-	-	-	-	2 (<1-19)	2 (<1-20)
Previous anti-angiogenic therapy, n (%)	Sunitinib: 124 (45) Sorafenib: 81 (29) Both: 72 (26)	Sunitinib: 60 (43) Sorafenib: 43 (31) Both: 36 (26)	-	-	-	-

Abbreviations in table: IMDC, International Metastatic Renal Cell Carcinoma Database; MSKCC, Memorial Sloan Kettering Cancer Centre; PS, performance status.
Notes: [a], patients receiving treatment at second-line.

Table 72. Characteristics of participants in TIVO-1, VEG105192 and Yang 2003 (reproduced from CS, Appendix 5, pg 97-99, Table 11, Section 4.10)

	TIVO-1[a]		VEG105192[a]		Yang 2003		
Baseline characteristic	**Tivozanib (n=260)**	**Sorafenib (n=257)**	**Pazopanib (n=290)**	**Placebo (n=145)**	**Bevacizumab 10mg (n=39)**	**Bevacizumab 3mg (n=37)**	**Placebo (n=40)**
Age, median years (range)	59 (23-83)	59 (23-85)	59 (28-85)	60 (25-81)	53	54	53
Gender, male n (%)	185 (71)	189 (74)	198 (68)	109 (75)	29 (74)	31 (84)	27 (68)
Race, Caucasian n (%)	249 (96)	249 (97)	252 (87)	122 (84)	-	-	-
MSKCC risk group, n (%)	Favourable: 780 (27) Intermediate: 173 (67) Poor: 17 (7)	Favourable: 87 (34) Intermediate: 160 (62) Poor: 10 (4)	Favourable: 113 (39) Intermediate: 159 (55) Poor: 9 (3) Unknown: 9 (3)	Favourable: 57 (39) Intermediate: 77 (53) Poor: 5 (3) Unknown: 6 (4)	-	-	-

	TIVO-1[a]		VEG105192[a]		Yang 2003		
Baseline characteristic	**Tivozanib (n=260)**	**Sorafenib (n=257)**	**Pazopanib (n=290)**	**Placebo (n=145)**	**Bevacizumab 10mg (n=39)**	**Bevacizumab 3mg (n=37)**	**Placebo (n=40)**
IMDC risk group, n (%)	-	-	-	-	-	-	-
Karnofsky PS, n (%)	-	-	-	-	-	-	-
Common metastasis site, n (%)	Lung: 212 (82) Lymph nodes: 182 (70) Adrenal gland: 78 (30) Liver: 67 (26) Bone: 61 (23)	Lung: 204 (79) Lymph nodes: 166 (65) Adrenal gland: 57 (22) Liver: 49 (19) Bone: 52 (20)	Lung: 214 (74) Lymph nodes: 157 (54) Bone: 81 (28) Liver: 75 (26) Kidney: 66 (23)	Lung: 106 (73) Lymph nodes: 86 (59) Bone: 38 (26) Liver: 32 (22) Kidney: 36 (25)	Liver: 10 (25.6) Bone: 2 (5.1)	Liver: 10 (27) Bone: 3 (8.1)	Liver: 10 (25) Bone: 6 (15)
Previous nephrectomy, n (%)	260 (100)	257 (100)	258 (89)	127 (88)	35 (90)	33 (89)	38 (95)
Time from initial diagnosis to randomisation, median months (range)	<12: 109 (42) >12: 137 (53)	<12: 105 (41) >12: 137 (53)	-	-	<12: 14 (35.9) 12-24: 8 (20.5) >24: 17 (43.6)	<12: 13 (35.1) 12-24: 6 (16.2) >24: 18 (46.2)	<12: 12 (30) 12-24: 9 (22.5) >24: 19 (47.5)
Previous anti-angiogenic therapy, n (%)	-	-	-	-	IL-2: 37 (95)	IL-2: 34 (92)	IL-2: 37 (93)

Abbreviations in table: IL-2, interleukin-2; IMDC, International Metastatic Renal Cell Carcinoma Database; MSKCC, Memorial Sloan Kettering Cancer Centre; PS, performance status.
Notes: [a], ITT population, mixed in regard to treatment history.

10.4 Secondary data sources

Table 73. Secondary data sources for RCTs included in the NMA

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
AXIS							
Motzer 2015	Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial	2011	The Lancet Oncology	14	6	552	562
Escudier 2014	Axitinib versus sorafenib in advanced renal cell carcinoma: Sub-analyses by prior therapy from a randomised phase III trial	2014	British Journal of Cancer	110	12	2821	2828
Ueda 2013	Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: Subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial	2013	Japanese Journal of Clinical Oncology	43	6	616	628
Escudier 2012	Updated results of the phase 3 AXIS trial: Axitinib vs sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC)	2012	European Urology, Supplements	11	1	e81	e81a
Rini 2012	Phase III AXIS trial for second-line metastatic renal cell carcinoma (mRCC): Effect of prior first-line treatment duration and axitinib dose titration on axitinib efficacy	2012	Journal of Clinical Oncology	30	5		
Dror 2012	Phase III AXIS trial of axitinib versus sorafenib in metastatic renal cell carcinoma: Updated results among cytokine-treated patients	2012	Journal of Clinical Oncology	30	15		
Cella 2011	Time to deterioration (TTD) in patient-reported outcomes in phase 3 axis trial of axitinib vs sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC)	2011	European Journal of Cancer	47		S224	
Alam 2012	Progression free survival vs overall survival: An example from randomised phase III trial with axitinib (AXIS) in metastatic renal cell carcinoma	2012	Asia-Pacific Journal of Clinical Oncology	8		306	
Escudier 2013	Safety and efficacy of second-line axitinib versus sorafenib in metastatic renal cell carcinoma by duration of prior therapy: Sub-analyses from a phase III trial	2013	European Journal of Cancer	49		S673	S674
Rini 2012	Erratum: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial (Lancet (2011) 378 (1931-39))	2012	The Lancet	380	9856	1818	
Motzer 2012	Axitinib vs sorafenib for advanced renal cell carcinoma: Phase III overall survival results and analysis of prognostic factors	2012	Annals of Oncology	23		ix262	

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Uemura 2012	Phase III axis trial of axitinib versus sorafenib in patients with metastatic renal cell carcinoma: Asian subgroup analysis	2012	Annals of Oncology	23		xi6	
Escudier 2011	Association of single nucleotide polymorphisms (SNPs) in VEGF pathway genes with progression-free survival (PFS) and blood pressure (BP) in metastatic renal cell carcinoma (mRCC) in the phase 3 trial of axitinib versus sorafenib (AXIS trial)	2011	European Journal of Cancer	47		S505	
Rini 2011	Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial	2011	Journal of Clinical Oncology	29	15		
Sherman 2014	A weighted-adjusted indirect comparison of everolimus (EVE) versus axitinib (AXI) in second-line metastatic renal cell carcinoma (mRCC) patients who previously failed sunitinib therapy	2014	Journal of Clinical Oncology	32	4		
Abraham 2012	Axitinib and sorafenib in second-line treatment of advanced renal cell carcinoma	2012	Community Oncology	9	7	214	215
Cella 2013	Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: Phase III (AXIS) trial	2013	British Journal of Cancer	108	8	1571	1578
Rini 2014	Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial	2014	Targeted Oncology			1	9
Tang 2014	Interpreting overall survival results when progression-free survival benefits exist in today's oncology landscape: A metastatic renal cell carcinoma case study	2014	Cancer Management and Research	6		365	371
Escudier 2014	Genotype correlations with blood pressure and efficacy outcomes from the randomized phase III AXIS trial of second-line axitinib versus sorafenib in metastatic renal cell carcinoma	2014	Journal of clinical oncology	32			
Motzer 2012	Axitinib vs sorafenib for advanced renal cell carcinoma: phase iii OS results and analysis of prognostic factors	2012	Annals of oncology	23			
Proskorovsky 2012	Axitinib (AXI) and best supportive care (BSC) in the treatment of sunitinib-refractory patients with metastatic renal cell carcinoma (MRCC): Results of a simulated treatment comparison (STC) analyses	2012	Value in health	15	7		
RECORD-1							
Motzer 2010	Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors.	2010	Cancer	116	18	4256	65
Tsukamoto	Phase III trial of everolimus in metastatic renal cell carcinoma: Subgroup	2011	Japanese Journal of	41	1	17	24

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
2011	analysis of Japanese patients from RECORD-1		Clinical Oncology				
Porta 2012	Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: An exploratory analysis of the outcomes of elderly patients in the RECORD-1 trial	2012	European Urology	61	4	826	833
Osanto 2010	Efficacy and safety of everolimus in elderly patients (pts) with metastatic renal cell carcinoma (mRCC)	2010	Journal of Clinical Oncology	28	15		
Bracarda 2012	Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: A RECORD-1 subgroup analysis	2012	British Journal of Cancer	106	9	1475	1480
Blesius 2013	Are tyrosine kinase inhibitors still active in patients with metastatic renal cell carcinoma previously treated with a tyrosine kinase inhibitor and everolimus? Experience of 36 patients treated in France in the RECORD-1 trial	2013	Clinical Genitourinary Cancer	11	2	128	133
Korhonen 2012	Correcting overall survival for the impact of crossover via a rank-preserving structural failure time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma	2012	Journal of Biopharmaceutical Statistics	22	6	1258	1271
Stein 2013	Survival prediction in everolimus-treated patients with metastatic renal cell carcinoma incorporating tumor burden response in the RECORD-1 trial	2013	European Urology	64	6	994	1002
Hutson 2009	Randomized, placebo-controlled, phase 3 study of everolimus, a novel therapy for patients with metastatic renal cell carcinoma: Subgroup analysis of patients progressing on prior bevacizumab therapy	2009	European Journal of Cancer, Supplement	7	03-Feb	434	
Calvo 2012	Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study	2012	European Journal of Cancer	48	3	333	339
Stein 2012	Dynamic tumor modeling of the dose-response relationship for everolimus in metastatic renal cell carcinoma using data from the phase 3 RECORD-1 trial	2012	BMC Cancer	12			
Thiam 2010	Determination of a new RECIST threshold using everolimus treatment in metastatic renal cell carcinoma: Evaluation from the RECORD-1 study	2010	Annals of Oncology	21		viii74	viii75
Wiederkehr 2009	Overall survival among metastatic renal cell carcinoma patients corrected for crossover using inverse probability of censoring weights: Analyses from the everolimus phase III trial	2009	European Journal of Cancer, Supplement	7	03-Feb	432	
Escudier 2008	Phase-3 randomised trial of everolimus (RAD001) vs placebo in metastatic renal cell carcinoma	2008	Annals of Oncology	19	S8	viii45	
Kay 2009	Updated data from a phase 3 trial of everolimus (RAD001) versus placebo in	2009	European Urology,	8	4	185	

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
	patients with metastatic renal cell carcinoma		Supplements				
Figlin 2012	Subgroup analysis of the phase 3 RECORD-1 trial of everolimus in patients with metastatic renal cell carcinoma: 1 versus 2 prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies	2012	BJU International	109		4	5
Porta 2011	Analysis of the relationship between Karnofsky performance status (KPS) and tumor response in the RECORD-1 phase III trial of everolimus in patients with advanced renal cell carcinoma (RCC)	2011	Journal of Clinical Oncology	29	15		
Stein 2011	Dynamic tumor modelling of the RECORD-1 phase III trial of everolimus quantifies relationship between dose and tumor growth in metastatic renal cell carcinoma	2011	European Urology, Supplements	10	2	232	
Calvo 2010	Everolimus (EVE) in record-1 elderly patients (PTS) with metastatic renal cell carcinoma (MRCC) and management of related adverse events (AES)	2010	European Urology, Supplements	9	2	63	64
Korhonen 2009	Overall survival among metastatic renal cell carcinoma (MRCC) patients corrected for crossover using a rank preserving structural failure time (RPSFT) model: Analyses from the everolimus phase III trial	2009	European Journal of Cancer, Supplement	7	03-Feb	440	
Calvo 2012	Survival among Advanced Renal Cell Carcinoma (ARCC) patients with >2 prior targeted therapies	2012	Annals of Oncology	23		ix272	
Bracarda 2010	Randomized, placebo-controlled, phase 3 study of everolimus in patients with metastatic renal cell carcinoma (mRCC): Subgroup analysis of patients intolerant of prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) thera	2010	Annals of Oncology	21		viii292	
Ravaud 2009	Subgroup analysis of French patients from RECORD-1: A randomized, placebo-controlled, phase III study of everolimus, a novel therapy for patients with metastatic renal cell carcinoma	2009	European Journal of Cancer, Supplement	7	03-Feb	440	441
Antoun 2011	Effect of everolimus an anti mTOR therapy, on skeletal muscle wasting in patients with metastatic renal cell carcinoma (MRCC)	2011	Supportive Care in Cancer	19	2	S161	
Di Lorenzo 2011	An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples	2011	Expert Opinion on Pharmacotherapy	12	10	1491	1497
Lamuraglia 2011	Interest of CHOI and modified CHOI criterion for evaluation of metastatic renal cell carcinomas (mRCC) patients treated with everolimus	2011	European Journal of Cancer	47		S169	
Albiges 2009	Interstitial pneumonitis during RAD-001 treatment: Incidence by blinded radiological analysis	2009	European Journal of Cancer, Supplement	7	03-Feb	427	

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Korhonen 2010	Overall survival (OS) of metastatic renal cell carcinoma (mRCC) patients corrected for crossover using inverse probability of censoring weights (IPCW) and rank preserving structural failure time (RPSFT) models: Two analyses from the RECORD-1 trial	2010	Journal of Clinical Oncology	28	15		
Kovalchik 2010	A one-sample progression-free survival (PFS) hazard ratio estimate for planning a randomized phase II study (RP2) in mRCC utilizing evidence from RECORD-1	2010	Journal of Clinical Oncology	28	15		
Zuber 2010	Correcting overall survival (OS) effect for the impact of crossover via rank preserving structural failure time (RPSFT) model: Case of mRCC RECORD-1 trial of everolimus (EVE)	2010	Journal of Clinical Oncology	28	15		
Calvo 2010	Phase 3 record-1 study of everolimus in metastatic renal cell carcinoma (mRCC): Subgroup analysis of patients (PTS) with 1 versus 2 prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) therapies	2010	Annals of Oncology	21		viii285	
Wiederkehr 2009	Therapeutic care in metastatic renal cell carcinoma during the follow-up phase of the RECORD-1 phase III trial	2009	Journal of Clinical Oncology	27	15	e17531	
Blesius 2010	Are TKIs still active in patients treated with TKI and everolimus? Experience from 36 patients treated in France in the record 1 trial	2010	Annals of Oncology	21		viii284	
Stein 2011	Quantifying the effect of everolimus on both tumor growth and new metastases in metastatic renal cell carcinoma (RCC): A dynamic tumor model of the RECORD-1 phase III trial	2011	Journal of Clinical Oncology	29	15		
Figlin 2011	Everolimus in metastatic renal cell carcinoma (mRCC): Subgroup analysis of patients (pts) with one versus two prior vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) therapies enrolled in the phase III RECORD-1 study	2011	Journal of Clinical Oncology	29	7		
Oudard 2011	Everolimus in patients with metastatic renal cell carcinoma: Subgroup analysis of patients with a reduction in tumor burden enrolled in a randomized, placebo-controlled, phase III trial	2011	European Urology, Supplements	10	2	229	
Hutson 2011	Phase III, randomized, placebo-controlled study of everolimus in patients with metastatic renal cell carcinoma (mRCC): Subgroup analysis of patients intolerant of prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) the	2011	Journal of Clinical Oncology	29	7		
Albiges 2011	Effect of everolimus therapy on skeletal muscle wasting in patients with metastatic renal cell carcinoma (mRCC): Results from a placebo-controlled	2011	Journal of Clinical Oncology	29	7		

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
	study						
Ravaud 2008	RAD001 plus best supportive care (BSC) vs BSC plus placebo in patients with metastatic renal cell carcinoma (RCC), that has progressed on VEGFr-TKI therapy: Results from a randomized, double-blind, multicenter phase III study [abstract no. LBA5026]	2008	Journal of Clinical Oncology: ASCO annual meeting proceedings	26	15S part I	256	
Antoun 2011	Impact of targeted therapies on muscle loss and adipose tissue in metastatic renal cell carcinoma (mRCC)	2011	European Journal of Cancer	47		S522	S523
Stein 2012	A dynamic tumor model of the RECORD-1 phase 3 trial in patients with metastatic renal cell carcinoma (mRCC): Quantification of the effect of everolimus on tumor growth and new metastases	2012	BJU International	109		11	
Oudard 2008	RAD001 vs placebo in patients with metastatic renal cell carcinoma after progression on VEGFr-TKI therapy: results from a randomized, double-blind, multicenter phase-III study	2008	Journal of clinical oncology	26 suppl		Abstract LBA5026	
Porta 2012	Relationship between Karnofsky performance status (KPS) and tumor response: Analysis of the RECORD-1 phase 3 trial of everolimus in patients with advanced renal cell carcinoma (RCC)	2012	BJU International	109		9	10
Oudard 2012	Optimisation of the tumour response threshold in patients treated with everolimus for metastatic renal cell carcinoma: Analysis of response and progression-free survival in the RECORD-1 study	2012	European Journal of Cancer	48	10	1512	1518
Oudard 2013	Relationship between biomarkers and everolimus efficacy in the phase III RECORD-1 trial of patients with metastatic renal cell carcinoma (mRCC).	2013	Journal of clinical oncology	31	Suppl 6		
Oudard 2012	Biomarkers of everolimus efficacy in patients with metastatic renal cell carcinoma (MRCC): analysis of the phase III record-1 trial	2012	Annals of oncology	23	9		
Wong 2013	Survival following initiation of everolimus for second-line treatment of metastatic renal cell carcinoma: Prognostic factors in clinical practice and comparison to clinical trials	2013	Journal of clinical oncology	31	15		
Hoaglin 2013	An indirect comparison of everolimus versus sorafenib in metastatic renal cell carcinoma- a flawed analysis and a problematic response	2013	Expert Opinion on Pharmacotherapy	14	12	1705	1706
TARGET							
Escudier 2009	Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial	2009	Journal of Clinical Oncology	27	20	3312	3318

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Choueiri 2013	Carbonic anhydrase IX as a potential biomarker of efficacy in metastatic clear-cell renal cell carcinoma patients receiving sorafenib or placebo: Analysis from the treatment approaches in renal cancer global evaluation trial (TARGET)	2013	Urologic Oncology: Seminars and Original Investigations	31	8	1788	1793
Negrier 2010	Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a sub-analysis of TARGET	2010	Medical Oncology	27	3	899	906
Pena 2010	Biomarkers predicting outcome in patients with advanced renal cell carcinoma: Results from sorafenib phase III treatment approaches in renal cancer global evaluation trial	2010	Clinical Cancer Research	16	19	4853	4863
Kane 2006	Sorafenib for the treatment of advanced renal cell carcinoma	2006	Clinical Cancer Research	12	24	7271	7278
Eisen 2008	Sorafenib for older patients with renal cell carcinoma: Subset analysis from a randomized trial	2008	Journal of the National Cancer Institute	100	20	1454	1463
Qu 2012	Carbonic anhydrase IX (CAIX) as a potential biomarker of efficacy in metastatic clear-cell renal cell carcinoma (mccRCC) in patients (pts) receiving sorafenib: Analysis of a randomized controlled trial (TARGET)	2012	Journal of Clinical Oncology	30	5		
Hutson 2010	Long-term safety of sorafenib in advanced renal cell carcinoma: Follow-up of patients from phase III TARGET	2010	European Journal of Cancer	46	13	2432	2440
Gschwend 2010	Efficacy and safety of sorafenib in patients with advanced clear-cell renal-cell carcinoma (RCC) with bone metastases: Results from the phase III TARGET study	2010	Onkologie	33	6	130	131
Bukowski 2009	Efficacy and safety of sorafenib in patients with advanced clear-cell renal-cell carcinoma (RCC) with bone metastases: Results from the phase III target study	2009	European Journal of Cancer, Supplement	7	03-Feb	432	
Crona 2012	Novel prognostic and predictive germline genetic markers of overall survival in renal cell carcinoma patients treated with sorafenib	2012	European Journal of Cancer	48		153	
Jager 2009	PREDICT (Patient characteristics in REnal cell carcinoma and Daily practICe Treatment with Nexavar) global non-interventional study: First interim results	2009	European Journal of Cancer, Supplement	7	03-Feb	431	432
Szczylik 2007	Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: survival and biomarker analysis	2007	Journal of clinical oncology	25 suppl		Abstract 5023	

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Ferte 2012	The use of tumor growth rate (TGR) in evaluating sorafenib and everolimus treatment in mRCC patients: An integrated analysis of the TARGET and RECORD phase III trials data	2012	Journal of Clinical Oncology	30	15		
Escudier 2006	Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): Impact of crossover on survival	2006	Journal of Clinical Oncology: ASCO annual meeting proceedings	24	18S	4524	
Massard 2010	Incidence of brain metastases in renal cell carcinoma treated with sorafenib	2010	Annals of Oncology	21	5	1027	1031
Sharma 2010	VEGF pathway therapy: Resampling positive phase III data to assess phase II trial designs and endpoints	2010	Journal of Clinical Oncology	28	15		
Maitland 2013	Estimation of renal cell carcinoma treatment effects from disease progression modeling	2013	Clinical Pharmacology and Therapeutics	93	4	345	351
Ferte 2014	Tumor growth rate provides useful information to evaluate Sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: An integrated analysis of the TARGET and RECORD phase 3 trial data	2014	European Urology	65	4	713	720
Trump 2007	Sorafenib in advanced clear-cell renal-cell carcinoma	2007	Urologic Oncology: Seminars and Original Investigations	25	5	443	445
Oudard 2009	Efficacy and safety of sorafenib in patients with advanced clear-cell renal cell carcinoma (RCC) with diabetes: Results from the phase III TARGET study	2009	Journal of Clinical Oncology	27	15	e16099	
Hutson 2009	Long-term safety of sorafenib (SOR) for the treatment (tx) of advanced clear-cell renal-cell carcinoma (RCC): Data analysis from patients (pts) treated for over 1 year in the phase III TARGET study	2009	Journal of Clinical Oncology	27	15	e16057	
Siebels 2005	Randomized phase III trial of the multiple kinase inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC)	2005	Onkologie	28	Suppl 3	1	
Bukowski 2005	Randomized Phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC) [abstract]	2005	Annual Meeting Proceedings of the American Society of Clinical Oncology	23		380	
Bellmunt 2007	Sorafenib TARGET trial results in Spanish patients	2007	Clinical and Translational	9	10	671	673

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
			Oncology				
Antoun 2013	Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies	2013	Cancer	119	18	3377	3384
Autier 2008	Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor	2008	Archives of Dermatology	144	7	886	892
CRECY							
Negrier 1998	Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma	1998	New England Journal of Medicine	338	18	1272	1278
TIVO-1							
Hutson 2013	Fewer dose adjustments with tivozanib vs. sorafenib in the phase III TIVO-1 study in advanced renal cell carcinoma (RCC)	2013	Urologe - Ausgabe A	52	1	89	90
Hutson 2013	Rates of dose adjustment in patients treated with tivozanib versus sorafenib in the phase III TIVO-1 study	2013	Journal of Clinical Oncology	31	15		
Motzer 2013	Overall survival results from a phase III study of tivozanib hydrochloride versus sorafenib in patients with renal cell carcinoma	2013	Journal of Clinical Oncology	31	6		
Hutson 2013	Subgroup analyses of a phase III trial comparing tivozanib hydrochloride versus sorafenib as initial targeted therapy for patients (pts) with metastatic renal cell carcinoma (mRCC)	2013	Journal of Clinical Oncology	31	6		
Sternberg 2013	Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study	2013	Journal of Clinical Oncology	31	15	Suppl 1	
Eisen 2012	Detailed comparison of the safety of tivozanib versus sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) from a Phase III trial	2012	BJU International	110		16	
Motzer 2011	A phase III, randomized, controlled study to compare tivozanib with sorafenib in patients (pts) with advanced renal cell carcinoma (RCC)	2011	Journal of Clinical Oncology	29	7		
Eisen 2012	Detailed comparison of the safety of tivozanib versus sorafenib in patients with advanced/ metastatic renal cell carcinoma (MRCC) from a phase 3 trial	2012	Annals of oncology	23	9		
Ratain 2006							
Ratain 2006	Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma	2006	Urologic Oncology: Seminars and Original Investigations	24	6		

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Jain 2006	Randomized discontinuation trial of sorafenib (BAY 43-9006)	2006	Cancer Biology and Therapy	5	10	1270	1272
RECORD-3							
Knox 2010	First-line everolimus followed by second-line sunitinib versus the opposite treatment sequence in patients with metastatic renal cell carcinoma (mRCC)	2010	Journal of clinical oncology	28	15		
Motzer 2013	Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC)	2013	Journal of clinical oncology	31	15	Suppl1	
Voss 2014	Identification and validation of predictive biomarkers (BM) for everolimus (EVE) in metastatic renal cell carcinoma: Analysis of 442 patients on RECORD-3	2014	Journal of clinical oncology	32	5S		
Hollaender 2010	A proof-of-concept (PoC) phase II criterion in a noninferiority context with application in patients with metastatic renal cell carcinoma (mRCC)	2010	Journal of Clinical Oncology	28	15		
Walter 2012							
Reinhardt 2010	Results of a randomized phase II study investigating multipeptide vaccination with IMA901 in advanced renal cell carcinoma (RCC)	2010	Journal of Clinical Oncology	28	15		
Singh 2010	Correlation of immune responses with survival in a randomized phase II study investigating multipeptide vaccination with IMA901 plus or minus low-dose cyclophosphamide in advanced renal cell carcinoma (RCC)	2010	Journal of Clinical Oncology	28	15		
Brugger 2010	Survival update of a randomized phase 2 study (IMA901-202) investigating therapeutic vaccination with multiple tumor-associated peptides (TUMAP) in renal cell carcinoma (RCC) patients after failure of previous therapy with cytokines or kinase inhibitors	2010	Annals of Oncology	21		viii273	
Walter 2011	Multiple distinct populations of myeloid derived suppressor cells in IMA901 treated renal cell cancer patients correlate with survival and with T-cell dysfunctions	2011	Cancer Research	71	8		
Walter 2010	Assessing and countering negative immune regulation in renal cell cancer patients-results of a randomized phase II trial with IMA901	2010	Journal of Immunotherapy	33	8	873	874
GOLD							
Motzer 2013	Phase 3 trial of dovitinib vs sorafenib in patients with metastatic renal cell carcinoma after 1 prior VEGF pathway-targeted and 1 prior mTOR inhibitor therapy	2013	European Journal of Cancer	49		S15	S16

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
Motzer 2012	Phase III trial of dovitinib (TKI258) versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies	2012	Journal of Clinical Oncology	30	15		
Motzer 2012	A multicenter, open-label, randomized phase 3 trial comparing the safety and efficacy of dovitinib (TKI258) versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies	2012	BJU International	109		7	8
Escudier 2014	Biomarker analysis from a phase III trial (GOLD) of dovitinib (Dov) versus sorafenib (Sor) in patients with metastatic renal cell carcinoma after one prior VEGF pathway-targeted therapy and one prior mTOR inhibitor therapy	2014	Journal of Clinical Oncology	32	4		
SWITCH							
Eichelberg 2012	Phase III randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO) followed by sunitinib (SU) vs. sunitinib followed by sorafenib in patients with advanced/meta-static renal cell carcinoma (mRCC) without prior systemic thera	2012	Urologe - Ausgabe A	51		35	
Michel 2014	SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC)	2014	Journal of Clinical Oncology	32	4		
Fischer 2012	Phase III randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO) followed by sunitinib (SU) versus sunitinib followed by sorafenib in patients with advanced / metastatic renal cell carcinoma without prior systemic therapy	2012	Onkologie	35		237	
Michel 2012	Phase III randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO) followed by sunitinib (SU) versus sunitinib followed by sorafenib in patients with advanced/metastatic renal cell carcinoma without prior systemic therapy	2012	Journal of Clinical Oncology	30	15		
VEG105192 trial							
Sternberg 2013	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	2013	European Journal of Cancer	49	6	1287	1296
Sternberg 2009	A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC)	2009	Journal of Clinical Oncology	27	15	5021	
Sternberg 2009	Predictive and prognostic factors in a phase III study of pazopanib in patients	2009	European Journal of	7	03-	424	

Study name	Title	Pub date	Journal name	Volume	Issue	Start page	End page
	with advanced renal cell carcinoma (RCC)		Cancer, Supplement		Feb		
Liu 2011	Baseline (BL) IL-6, IL-8, and VEGF as predictive and prognostic markers for overall survival (OS) in metastatic renal cell carcinoma (mRCC) patients (pts) treated in a phase iii trial of pazopanib (PAZO) versus placebo (PL)	2011	European Journal of Cancer	47		S170	
De 2009	Pazopanib in renal cell carcinoma: Efficacy and safety in Phase II and III trials	2009	Asia-Pacific Journal of Clinical Oncology	5		A147	
DISRUPTOR							
Sarantopoulos 2013	A phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC) patients: Updated phase I results of the Disruptor-1 trial.	2013	Journal of clinical oncology	31			

10.5 Company's search strategy

Table 74. Search strategy for the Embase platform

#	Search History	Results
1	'prospective study'/exp	264,059
2	'clinical trial'/exp	988,717
3	'randomization'/de	63,751
4	'controlled study'/de	4,442,263
5	'single blind procedure'/de	18,822
6	'double blind procedure'/de	117,811
7	'crossover procedure'/de	40,544
8	'placebo'/de	261,015
9	'clinical trial' OR 'clinical trials'	1,188,196
10	'controlled clinical trial' OR 'controlled clinical trials'	369,859
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'	445,415
12	'randomisation' OR 'randomization' OR random*	1,063,588
13	rct	17,928
14	'random allocation' OR 'random assignment'	3,445
15	'randomly allocated' OR 'randomly assigned'	101,881
16	'allocated randomly' OR 'assigned randomly'	6,386
17	allocated NEAR/2 random OR assign* NEAR/2 random* OR randomi*	755,933
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	213,837
19	placebo*	339,531
20	'prospective study'/de	264,059
21	nrct OR 'n rct' OR n?rct OR non NEAR/2 random*	17,671
22	'controlled clinical trial'/exp OR 'intervention study'/exp	490,091
23	(clinical NEXT/1 trial*):ab,ti	296,297
24	'major clinical study'/exp	2,269,885
25	compar*:ab,ti OR group*:ab,ti	6,475,890
26	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'follow up'/exp OR 'clinical article'/exp	2,593,578
27	cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti	475,704
28	'open study'/exp	17,979
29	(case* NEXT/1 control*):ab,ti	100,627
30	'clinical article'/exp OR 'survival'/exp OR 'case control study'/exp	2,112,152
31	'comparative study'/de	638,449
32	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	11,586,351
33	'case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de	2,761,293
34	#32 NOT #33	11,156,742

#	Search History	Results
35	'kidney carcinoma'/syn OR 'kidney metastasis'/exp	54,589
36	'kidney tumor'/syn OR 'kidney adenoma'/exp	100,751
37	renal*:ab,ti OR kidney*:ab,ti OR grawit*:ab,ti OR hypernephroid*:ab,ti OR nephroid*:ab,ti	845,165
38	carcinoma*:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR adeno*:ab,ti OR pyelocarcinoma*:ab,ti OR oncocytoma:ab,ti	2,192,632
39	metastasis:ab,ti OR metastases:ab,ti	299,561
40	tumor*:ab,ti OR tumour*:ab,ti	1,499,608
41	#38 OR #39 OR #40	2,931,618
42	#37 AND #41	133,163
43	(metanephric NEAR/2 adeno*):ab,ti	220
44	rcc:ab,ti OR mrcc:ab,ti OR 'm-rcc':ab,ti	15,301
45	'hypernephroma':ab,ti	1,324
46	#35 OR #36 OR #42 OR #43 OR #44 OR #45	173,315
47	'bevacizumab'/syn OR avastin OR 'nsc 704865' OR nsc704865 OR 'anti-vegf' OR 'rhumab-vegf'	35,781
48	'interleukin-2'/syn OR 'biotest' OR bioleukin OR 'interleukin-ii' OR 'il-2' OR il2 OR 'ro-236019' OR tcgf OR tsf	110,974
49	'everolimus'/syn OR afinitor OR certican OR 'nvp-rad-001' OR 'rad-001' OR 'rad 001a' OR rad001 OR rad001a OR 'sdz rad'	15,086
50	'temsirolimus'/syn OR 'cci-779' OR 'cell-cycle-inhibitor-779' OR 'nsc 683864' OR nsc683864 OR torisel	5,725
51	'sorafenib'/syn OR 'bay 43-9006' OR 'bay 439006' OR 'bay43-9006' OR bay439006 OR nexavar	16,386
52	'sunitinib'/syn OR sutent OR 'pha 2909040ad' OR 'pha2909040ad' OR 'su010398' OR 'su 011248' OR 'su 10398' OR su10398 OR 'su 11248' OR su010398 OR 'su011248' OR su11248	13,891
53	'pazopanib'/syn OR armala OR gw786034* OR gw NEXT/1 786034* OR sb NEXT/1 710468* OR sb710468* OR votrient	3,261
54	'axitinib'/syn OR 'ag 013736' OR 'ag 13736' OR ag013736 OR ag13736 OR inlyta	2,178
55	'tivozanib'/syn OR arthrovas OR neoretna OR neovastat OR provascar OR psovascar OR 'ae 941' OR ae941	782
56	'cediranib'/syn OR 'azd 2171' OR azd2171 OR recentin	1,983
57	'dovitinib'/syn OR 'chir 258' OR chir258 OR 'tki 258' OR tki258	548
58	'nivolumab'/syn OR 'bms 936558' OR bms936558 OR 'mdx 1106' OR mdx1106 OR 'ono 4538' OR ono4538	559
59	'alpha-interferon'/syn OR alfaferone OR alferon OR 'alpha ferone' OR cilferon OR ginterferon OR 'interferon-alpha' OR introma OR kemron OR leukinferon OR leukinferron OR 'leukocyte interferon' OR 'refecon a' OR 'referon a3' OR sumiferon OR sumipheron OR veldona	56,445
60	'cabozantinib'/syn OR 'bms-907351' OR 'xl184' OR 'cometriq' OR 'xl-184' OR 'bms907351' OR 'bms 907351'	974
61	'naptumomab estafenatox'/syn OR 'abr-217620'	30
62	'ima901'/exp	27
63	'bnc105p'/syn	33
64	'famitinib'/syn OR 'shr1020'	10

#	Search History	Results
65	'dalantercept'/syn OR 'ace-041'	32
66	'trc105'/exp	78
67	'apitolisib'/syn OR 'gdc-0980' OR 'gdc0980' OR 'gdc 0980' OR 'rg7422' OR 'rg-7422' OR 'rg 7422' OR 'gne 390' OR 'gne390' OR 'gne-390'	193
68	#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 #65 OR #66 OR #67	223,026
69	#34 AND #46 AND #68	12,606
70	#34 AND #46 AND #68 AND [animals]/lim	1,062
71	#34 AND #46 AND #68 AND ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)	685
72	#34 AND #46 AND #68 AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim)	228
73	#34 AND #46 AND #68 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)	4,209
74	#70 OR #71 OR #72 OR #73	5,344
75	#69 NOT #74	7,262
76	#69 NOT #74 AND [english]/lim	6,774

Table 75. Search straegy for the Cochrane library platform

No.	Query	Results
1	MeSH descriptor: [Carcinoma, Renal Cell] explode all trees	496
2	(renal* or kidney* or grawit* or hypernephroid* or nephroid*):ti,ab,kw	33,073
3	(carcinoma* or cancer* or neoplasm* or adeno* or tumo?r* or pyelocarcinoma* or metastas?s or oncocytoma): ti,ab,kw	87,789
4	#2 and #3	2,896
5	(metanephric near/2 aden*): ti,ab,kw	0
6	(rcc or mrcc or "m-rcc"): ti,ab,kw	337
7	hypernephroma: ti,ab,kw	4
8	#1 or #4 or #5 or #6 or #7	2,925
9	MeSH descriptor: [Interferon-alpha] explode all trees	2,582
10	MeSH descriptor: [Interleukin-2] explode all trees	811
11	(“alpha-interferon” or alfaferone or alferon or “alpha ferone” or cilferon or ginterferon or “interferon-alpha” or introma or kemron or leukinferon or leukinferron or “leukocyte interferon” or “refecon a” or “referon a3” or sumiferon or sumipheron or veldona or "Intron A" or Alfatronol or Glucoferon or Urifron or Roferon or Laroferon or Roceron): ti,ab,kw	4,277
12	(biotest or bioleukin or “interleukin-ii” or “interleukin-2” or “il-2” or il2 or “ro-236019” or tcgf or tsf or Proleukin or aldesleukin or "T cell growth factor"): ti,ab,kw	2,497
13	(everolimus or afinitor or affinitor or certican or “nvp-rad-001” or “rad-001” or “rad 001a” or rad001 or rad001a or “sdz rad” or votubia or xience or zortress): ti,ab,kw	683
14	(temsirolimus or “cci-779” or “cell-cycle-inhibitor-779” or “nsc 683864” or nsc683864 or torisel): ti,ab,kw	85
15	(bevacizumab or altuzan or avastin or “nsc 704865” or nsc704865 or “anti-vegf” or “rhumab-vegf”): ti,ab,kw	1,241
16	(sunitinib or sutent or “pha 2909040ad” or pha2909040ad or “su 010398” or “su 011248” or “su 10398” or su10398 or “su 11248” or su010398 or su011248 or su11248): ti,ab,kw	243

No.	Query	Results
17	(armala or pazopanib or gw786034* or sb710468* or votrient): ti,ab,kw	81
18	(axtinib or "ag 013736" or ag013736 or ag13736 or "ag 13736" or inlyta): ti,ab,kw	48
19	(“bay 43-9006” or “bay 439006” or “bay43-9006” or bay439006 or nexavar or sorafenib): ti,ab,kw	332
20	Cediranib:ab,ti,kw or "azd 2171":ab,ti,kw or azd2171:ab,ti,kw or recentin: ti,ab,kw	45
21	Tivozanib:ti,ab,kw	20
22	(cabozantinib or "bms-907351" or "xl184" or "cometriq" or "xl-184" or "bms907351" or "bms 907351"):ti,ab,kw	12
23	("naptumomab estafenatox" or "abr-217620"):ti,ab,kw	1
24	("IMA901"):ti,ab,kw	1
25	("famitinib" or "shr1020"):ti,ab,kw	1
26	("dalantercept" or "ace-041"):ti,ab,kw	0
27	("bnc105p"):ti,ab,kw	0
28	("trc105"):ti,ab,kw	0
29	("apitolisib" or "gdc-0980" or "gdc0980" or "gdc 0980" or "rg7422" or "rg-7422" or "rg 7422" or "gne 390" or "gne390" or "gne-390"):ti,ab,kw	2
30	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	8,990
31	#8 and #30 in Cochrane Reviews (Reviews and Protocols), Trials	591

Table 76: Search strategy for the PubMed platform

No	Query	Results
1	Search ((renal or kidney))	880,824
2	Search ((grawit or hypernephroid))	216
3	Search nephroid	12
4	Search (#1 OR #2 OR #3)	880,862
5	Search ((carcinoma or cancer or neoplasm or adenocarcinoma or tumour or tumor or pyelocarcinoma or metastasis or metastases or oncocytoma))	3,382,046
6	Search (#4 AND #5)	146,189
7	Search ((rcc or mrcc or m-rcc or hypernephroma or "metanephric adenocarcinoma"))	37,934
8	Search "renal cell carcinoma"	29,630
9	Search (#6 or #7 or #8)	147,338
10	Search (("Interferon alpha" or "Interferon-alpha" or "Interleukin 2" or "Interleukin-2" or "Interleukin ii" or "interleukin-ii"))	85,640
11	Search ((“alpha-interferon” or alfaferone or alferon or “alpha ferone” or cilferon or ginterferon or “interferon-alpha” or introma or kemron or leukinferon or leukinferron or “leukocyte interferon” or “refecon a” or “referon a3” or sumiferon or sumipheron or veldona or "Intron A" or Alfatronol or Glucoferon or Urifron or Roferon or Laroferon or Roceron))	35,150
12	Search ((biotest or bioleukin or “interleukin-ii” or “interleukin-2” or “il-2” or il2 or “ro-236019” or tcgf or tsf or Proleukin or aldesleukin or "T cell growth factor"))	73,941
13	Search ((everolimus or afinitor or affinitor or certican or “nvp-rad-001” or “rad-001” or “rad 001a” or rad001 or rad001a or “sdz rad” or votubia or xience or zortress))	3,562
14	Search ((temsirolimus or “cci-779” or “cell-cycle-inhibitor-779” or “nsc 683864” or nsc683864 or torisel))	1,122

No	Query	Results
15	Search ((bevacizumab or altuzan or avastin or “nsc 704865” or nsc704865 or “anti-vegf” or “rhumab-vegf”))	12,155
16	Search ((sunitinib or sutent or “pha 2909040ad” or pha2909040ad or “su 010398” or “su 011248” or “su 10398” or su10398 or “su 11248” or su010398 or su011248 or su11248))	2,525,208
17	Search ((armala or pazopanib or gw786034* or sb710468* or votrient))	632
18	Search ((axtinib or "ag 013736" or ag013736 or ag13736 or "ag 13736" or inlyta))	397
19	Search ((“bay 43-9006” or “bay 439006” or “bay43-9006” or bay439006 or nexavar or sorafenib))	30,647
20	Search ((Cediranib or "azd 2171" or azd2171 or recentin))	247
21	Search Tivozanib	49
22	Search ((cabozantinib or "bms-907351" or "xl184" or "cometriq" or "xl-184" or "bms907351" or "bms 907351"))	158
23	Search (("naptumomab estafenatox" or "abr-217620"))	9
24	Search “IMA901”	7
25	Search (("famitinib" or "shr1020"))	4
26	Search (("dalantercept" or "ace-041"))	2
27	Search “BNC105P”	3
28	Search “trc105”	41
29	Search (("apitolisib" or "gdc-0980" or "gdc0980" or "gdc 0980" or "rg7422" or "rg-7422" or "rg 7422" or "gne 390" or "gne390" or "gne-390"))	23
30	Search (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29)	2,659,459
31	Search (#9 AND #30)	39,122
32	Search (#31 AND (in process[sb] OR pubstatusaheadofprint))	305

10.6 Detailed modifications to the company’s model implemented by the ERG

Table 77. Detailed modifications to the company’s model implemented by the ERG

Sheet	Cell	Company’s value	ERG value
OS binding for PFS and TTD, nivolumab and everolimus			
PF Nivo	J19:J2105	=IF(TTD!CM29<PFS!BB32,TTD!CM29,PFS!BB32)	=IF(MIN(OS!CP31,TTD!CM29)<MIN(OS!CP31,PFS!BB32),MIN(OS!CP31,TTD!CM29),MIN(OS!CP31,PFS!BB32))
	K19:K2105	=IF(TTD!CM29>PFS!BB32,0,PFS!BB32-J19)	=IF(MIN(OS!CP31,TTD!CM29)>MIN(OS!CP31,PFS!BB32),0,MIN(OS!CP31,PFS!BB32)-J19)
	L19:L2109	=IF(TTD!CM29>PFS!BB32,TTD!CM29-PFS!BB32,0)	=IF(MIN(OS!CP31,TTD!CM29)>MIN(OS!CP31,PFS!BB32),MIN(OS!CP31,TTD!CM29)-MIN(OS!CP31,PFS!BB32),0)
	M19:M2109	=IF(TTD!CM29>PFS!BB32, OS!CP31-TTD!CM29,IF(OS!CP31-PFS!BB32<0,0,OS!CP31-PFS!BB32))	=1-J19-K19-L19-O19
	O19:O2109	=IF(PFS!BB32>OS!CP31,1-PFS!BB32,1-OS!CP31)	=1-OS!CP31
PF Ever	J19:J2105	=IF(TTD!CN29<PFS!BC32,TTD!C	=IF(MIN(OS!CQ31,TTD!CN29)<MIN(OS!CQ31,

Sheet	Cell	Company's value	ERG value
		N29,PFS!BC32)	PFS!BC32),MIN(OS!CQ31,TTD!CN29),MIN(OS!CQ31,PFS!BC32))
	K19:K2105	=IF(TTD!CN29>PFS!BC32,0,PFS!BC32-J19)	=IF(MIN(OS!CQ31,TTD!CN29)>MIN(OS!CQ31,PFS!BC32),0,MIN(OS!CQ31,PFS!BC32)-J19)
	L19:L2109	=IF(TTD!CN29>PFS!BC32,TTD!CN29-PFS!BC32,0)	=IF(MIN(OS!CQ31,TTD!CN29)>MIN(OS!CQ31,PFS!BC32),MIN(OS!CQ31,TTD!CN29)-MIN(OS!CQ31,PFS!BC32),0))
	M19:M2109	=IF(TTD!CN29>PFS!BC32, IF(OS!CQ31-TTD!CN29<0,OS!CQ31-TTD!CN29,OS!CQ31),IF(OS!CQ31-PFS!BC32<0,0,OS!CQ31-PFS!BC32))	=1-J19-K19-L19-O19
	O19:O2109	=IF(PFS!BC32>OS!CQ31,1-PFS!BC32,1-OS!CQ31)	=1-OS!CQ31
OS binding for PFS, axitinib and BSC			
Pf Axi	J19:J2105	=PFS!BM32	=MIN(PFS!BM32,OS!DC31)
	M19:M2109	=OS!DC31-PFS!BM32	=MAX(0,OS!DC31-PFS!BM32))
PF BSC	J19:J2105	=PFS!BL32	=MIN(PFS!BL32,OS!DB31)
	M19:M2109	=OS!DB31-PFS!BL32	=MAX(0,OS!DB31-PFS!BL32)
Abbreviations in table: Axi, axitinib; BSC, best supportive care; ERG, Evidence Review Group; Ever, everolimus; Nivo, nivolumab; OS, overall survival; PF, patient flow; PFS, progression-free survival; TTD, time to discontinuation.			

Nivolumab for previously treated advanced or metastatic renal cell carcinomaERRATUM

This report was commissioned by the NIHR HTA Programme as project number 15/06/13

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
1	Amended the text "The comparators of interest in the final scope issued by NICE are axitinib, everolimus (not recommended by NICE but until November 2015 it was funded by the Cancer Drugs Fund [CDF]) and best supportive care (BSC). The ERG therefore considers the comparator in CheckMate 025 (everolimus) to be in line with the NICE final scope" to "The comparators of interest in the final scope issued by NICE are axitinib, everolimus (not recommended by NICE but funded by the Cancer Drugs Fund [CDF]) and best supportive care (BSC)".
2	Amended the text "Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥5% incidence" to "Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥15% incidence"
3	Amended the text "In the NMA using ITT results for OS, [redacted]" to "In the NMA using ITT results for OS, [redacted]"
4	Amended the text "The relative effectiveness of everolimus and BSC was incorporated by applying the crossover-adjusted hazard ratios (HR) from the NMA to the OS curve of the everolimus arm in CheckMate 025, assuming BSC would be as effective as placebo" to "The relative effectiveness of axitinib and BSC was incorporated by applying the crossover-adjusted hazard ratios (HR) from the NMA to the OS curve of the everolimus arm in CheckMate 025, assuming BSC would be as effective as placebo". Amended the text "The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit sufficiently well the data, and explored more flexible models" to "The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit the PFS data sufficiently well, and explored more flexible models."
27	Amended the text "the justifications for inclusion of CheckMate 010 and CheckMate 003 was to provide supportive long term survival data (3 years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab" to "the justifications for inclusion of CheckMate 010 and CheckMate 003 was to provide supportive long term survival data (4 years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab".
41	Amended the source "Motzer *et al.* 2014[65]" to "Motzer *et al.* 2015[65]".
45	Amended the text "In CheckMate 003[66], ORR was observed in 29% (10/34) of advanced RCC patients treated with either nivolumab 1 mg/kg or 10 mg/kg; an additional 27% (9/34) of patients experienced stable disease lasting 24 weeks, and 10 out of 34 patients achieved complete or partial response at median duration of 12.9 months (80% CI: 8.4 to 29.1 months)" to "In CheckMate 003[66], ORR was observed in 29% (10/34) of advanced RCC patients treated with either nivolumab 1 mg/kg or 10 mg/kg; an additional 27% (9/34) of patients experienced stable disease lasting 24 weeks, and 10 out of 34 patients achieved complete or partial response at median duration of 12.9 months (range: 8.4 to 29.1+ months).
49	Amended the text "Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥5% incidence" to "Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥15% incidence"
52	Amended text "In addition, discontinuations due to TRAEs were >10% in both CheckMate 010 and CheckMate 003; and most importantly no deaths were reported due to nivolumab toxicity in CheckMate 010 or in advanced RCC patients in CheckMate 003" to "In addition, discontinuations due to TRAEs were <10% in both

Page No.	Change
	CheckMate 010 and CheckMate 003; and most importantly no deaths were reported due to nivolumab toxicity in CheckMate 010 or in advanced RCC patients in CheckMate 003".
62	Amended text "In the NMA, the ITT analysis of OS indicated that [redacted]"" to "In the NMA, the ITT analysis of OS indicated that [redacted]"
68	Removed the text "The ERG notes that the numbers of patients at risk reported by the company in Table 30 of the CS (and replicated in Table 27) did not correspond with the values included in the electronic model (not shown). However, the KM curves in the model were identical to the ones shown in Figure 24 of the CS (replicated in Figure 19)."
95	Amended the text "Not reported clearly. The company stated that, "The UK EQ-5D tariff was used to value patient questionnaire responses" (CS, pg 161, Section 5.4.1) but did not include references or additional details." to "Not reported in the CS. The company informed the ERG at a later stage that time trade-off was used."
112	Removed the text "No evidence was presented to support the different relative treatment effectiveness between the treatments, and the assumption was not stated"
116	Removed the text "However, the effect included in the model seems to contradict the company's statements, as it indicates that the HRQoL of patients who progressed in the nivolumab arm worsened more than in patients who progressed after treatment with everolimus, coeteris paribus. The ERG notes that the impact of this interactive effect is expected to be negligible given its effect size."

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company, Bristol-Myers Squibb (BMS), submitted clinical and economic evidence in support of the effectiveness of nivolumab for previously treated patients with advanced/metastatic renal cell carcinoma (RCC), to the National Institute for Health and Care Excellence (NICE).

At the time of writing the Evidence Review Group's (ERG) report, nivolumab has not been granted marketing authorisation in England. According to the company, marketing authorisation application was submitted to the European Medicine Agency (EMA) in October 2015. In addition, the Committee for Medical Products for Human Use (CHMP) gave a positive opinion on nivolumab on 25th February 2016.

The direct clinical evidence presented in the company's submission (CS) is derived from CheckMate 025, a phase III multicentre open-label randomised controlled trial (RCT). CheckMate 025 compared nivolumab with everolimus in patients with histologically confirmed advanced/metastatic renal cell carcinoma (RCC) who have received one or two previous anti-angiogenic agents.

The final scope issued by NICE specified the population of interest to be people with previously treated advanced/metastatic RCC. The ERG's clinical experts consider the population in CheckMate 025 to be reflective of patients in English clinical practice. The ERG therefore considers the population in CheckMate 025 to be relevant to the decision problem.

The intervention in CheckMate 025 was nivolumab, a fully human monoclonal immunoglobulin antibody that stops the evasion of immune-mediated tumour destruction and stimulates the patient's own immune system to directly destroy cancer cells, resulting in destruction of the tumour through pre-existing, intrinsic processes. The comparators of interest in the final scope issued by NICE are axitinib, everolimus (not recommended by NICE but funded by the Cancer Drugs Fund [CDF]) and best supportive care (BSC). The ERG therefore considers the comparator in CheckMate 025 (everolimus) to be in line with the NICE final scope.

In addition, all clinically relevant outcomes as specified in the NICE final scope including overall survival (OS), progression-free survival (PFS), response rate, adverse effects of treatment, and health-related quality of life (HRQoL) were reported in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary objective of CheckMate 025 was to evaluate the safety and efficacy of nivolumab in comparison with everolimus in patients with advanced RCC previously treated with anti-angiogenic

agents. To be eligible for enrolment, patients had to be aged ≥18 years with histologically confirmed advanced/metastatic RCC with a clear-cell component; measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1; disease progression during or after the last treatment regimen and within 6 months before study enrolment; and Karnofsky performance status ≥70%.

Patients in CheckMate 025 were randomised (1:1) to either nivolumab 3 mg/kg intravenously (IV) every 2 weeks (n=410) or to everolimus administered orally at a daily dose of 10 mg (n=411). Disease assessment was performed every 8 weeks for the first year, and then every 12 weeks until disease progression or discontinuation of treatment.

In CheckMate 025, overall survival (OS), defined as the time from randomisation to date of death, was significantly better in the nivolumab group compared with everolimus group (hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.57 to 0.93; p=0.002). Progression-free survival (PFS) was defined as the time from randomisation to first documented RECIST defined progression or death from any cause. Median PFS was not statistically significant between nivolumab (4.6 months, 95% CI: 3.7 to 5.4) and everolimus (4.4 months, 95% CI: 3.7 to 5.5) groups (HR 0.88, 95% CI: 0.75 to 1.03, p=0.11).

Objective response rate (ORR) in CheckMate 025 was defined as the number of patients with a complete or a partial response divided by the number of patients randomised. Investigator-assessed ORR using the RECIST criteria was significantly higher in the nivolumab (25%) compared with the everolimus group (5%) (odds ratio [OR] 5.98; 95% CI: 3.68 to 9.72; p<0.001). The ORR, with a confirmatory scan after ≥4 weeks (that is, confirmed ORR), was also significantly superior (p<0.001) in the nivolumab group (22%) compared with the everolimus group (4%).

Health-related quality of life (HRQoL) in CheckMate 025 (assessed using the FKSI-DRS) significantly improved in the nivolumab group compared with the everolimus group after the first year of treatment. In addition, a higher proportion of patients in the nivolumab group (55%) experienced meaningful improvement in FKSI-DRS (defined as ≥2 point increase) compared with 37% of patients in the everolimus group (p<0.001).

In CheckMate 025, more patients in the everolimus group than in the nivolumab group experienced at least one treatment-related adverse event (TRAE) (nivolumab 78.6% vs everolimus 87.9%), grade 3–4 TRAEs (nivolumab 19% vs everolimus 37%) and discontinuations due to TRAEs (nivolumab 7.6% vs everolimus 13.1%). Additionally, the incidence of select adverse events (defined as adverse events with potential immunological cause that is of special clinical interest with the use of nivolumab) with ≥15% incidence in the nivolumab group were skin (37.2%), gastrointestinal (GI) (24.4%), renal

(17.5%) and hepatic (16%), while in the everolimus group they were GIs (31.2%), pulmonary (18.6%) and skin (44.6%).

While CheckMate 025 compares nivolumab with everolimus, there are no head-to-head trials that compare nivolumab with the other treatments listed in the NICE final scope (i.e. axitinib and best supportive care [BSC]). The company therefore conducted an NMA.

In the NMA using ITT results for OS, [redacted] In the NMA using crossover-adjusted results for OS [redacted]

In the NMA for PFS, [redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* six-state model in Microsoft Excel® to assess the cost-effectiveness of nivolumab compared to everolimus, axitinib and best supportive care (BSC). The six health states were progression-free survival on treatment (PFST), progression-free survival off treatment (PFSN), post-progression survival on treatment (PPST), post-progression survival off treatment (PPSN), terminal care (TC) and death.

All patients started in the PFST health state, and could only transition to death through the TC tunnel state, which they were assumed to occupy in the eight weeks leading to death. The time horizon was set to 30 years. Weekly cycles were used, and no half-cycle correction was applied due to the short cycle length. Costs and quality adjusted life-years (QALYs) accrued were discounted at a rate of 3.5%.

An area under the curve (AUC) approach was adopted in the economic model, modelling the proportions of patients in each health state based on parametric survival curves for each clinical outcome. Overall survival (OS) was used to determine how many patients were dead or alive; progression-free survival (PFS) to determine the proportions of alive patients who had progressed or not; and time-to-discontinuation (TTD) data were used to inform the number of patients who were on or off treatment. OS, PFS and TTD were analysed independently. The comparison between

nivolumab and everolimus was informed by parametric survival analyses of OS, PFS and TTD data from the CheckMate 025 trial. A network meta-analysis (NMA) was carried out to estimate the relative treatment effects on OS and PFS between nivolumab and axitinib, and nivolumab and best supportive care (BSC), as no head-to-head evidence was available for these two comparisons.

Based on the CheckMate 025 trial data, a generalised gamma model was selected to extrapolate OS for nivolumab and everolimus, as it predicted survival in a plausible manner according to clinical expert opinion. The relative effectiveness of axitinib and BSC was incorporated by applying the crossover-adjusted hazard ratios (HR) from the NMA to the OS curve of the everolimus arm in CheckMate 025, assuming BSC would be as effective as placebo.

The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit the PFS data sufficiently well, and explored more flexible models. Spline-based survival models of Royston and Parmar were used to fit and extrapolated the CheckMate 025 PFS data. The PFS for axitinib and BSC was estimated by applying the HR estimated in the NMA to the everolimus curve, assuming that BSC was equally as effective as placebo.

The company used the same survival analysis approach to model TTD data for nivolumab and everolimus as for PFS, using spline-based models for nivolumab and everolimus. In the absence of TTD data for axitinib, the company assumed that treatment was continued until disease progression. As no treatment duration was associated to BSC, no assumption on TTD was necessary.

Pharmacological resource use for nivolumab, everolimus and axitinib was based on the treatment indications. The company assumed that the proportion of planned drug doses received observed in the trial would be applicable. The proportion of nivolumab and everolimus actually received by patients and thus assumed to be reimbursed by the NHS was based on data collected in the CheckMate 025 trial, and was equal to 92% and 94%, respectively. The proportion of planned axitinib received was 102%, based on the AXIS trial as reported in the single technology appraisal, “axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment” (TA 333). Patients were allowed to receive treatment after disease progression, in line with the clinical stopping rules of all the active interventions with the exception of axitinib, due to lack of TTD trial data.

Resource use in the progression-free and post-progression survival health states was assumed the same as that used in TA 333. Patients were assumed to require general practitioner (GP) visits once a month before and after progressing. They were also assumed to have monthly blood tests and a computerised tomography (CT) scan every 3 months before progression, 1.5 specialist palliative care nurse visits per month and to receive pain medication following disease progression. The cost of TC

randomisation, blinding, and withdrawal. However, the company supplemented the Jadad scale with an assessment of all items including in the NICE RCT checklist: allocation concealment, baseline characteristics, outcome selection and reporting, and statistical analysis. Of the nine trials informing the NMA had appropriate randomisation and allocation concealment procedures, and in four trials this was not adequately described. Baseline characteristics were well balanced in all trials, however, only four of the trials were double blind with the remaining five being open label. The company's assessment of RCTs included in the NMA is shown in Appendix **Error! Reference source not found.**.

4.1.5 Summary of review methods

The search for relevant RCTs was comprehensive and systematic, although it included several comparators outside of the NICE scope. However, this may have facilitated the creation of a complete network. The inclusion of trials was in line with the scope, however, the company excluded non-English language references and trials with a small sample size. In addition, some studies were excluded due to unclear line of therapy and unclear disease stage. As a result, the ERG is concerned that relevant studies may have been missed. The quality assessments of the included trials seem to have been done in accordance to standard criteria recommended by NICE.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

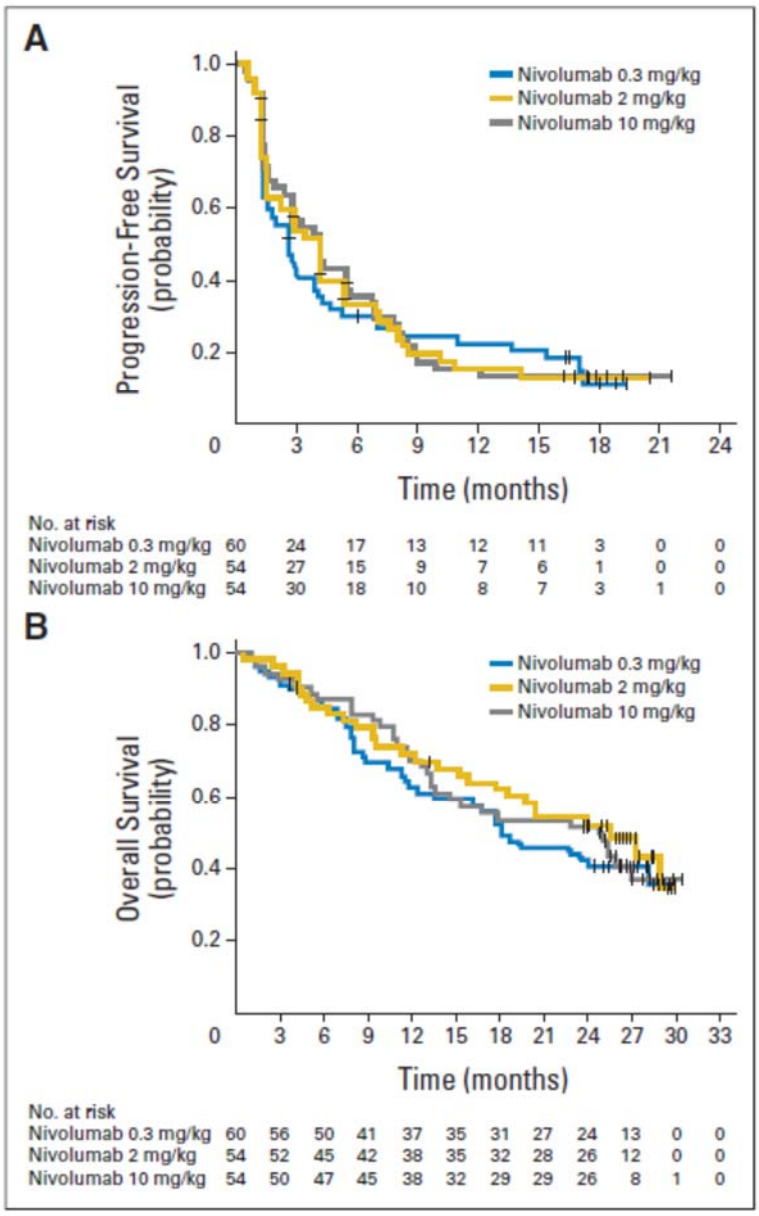
The company's systematic review of RCTs identified one trial[37, 39] comparing nivolumab with everolimus in patients with advanced clear-cell RCC who have been pre-treated with one or two regimens of anti-angiogenic therapy. According to the CS (pg 106, Section 4.11), the company did not conduct a systematic review to identify non-RCT evidence since RCT data are available for all comparators relevant for the decision problem. However, the company identified one randomised dose- ranging trial (CheckMate 010[65]) and one non-randomised dose escalation trial (CheckMate 003[66]) from its internal clinical trial database to supplement the RCT data in the use of nivolumab in advanced RCC.

Table 1 is a summary of CheckMate 025, CheckMate 010 and CheckMate 003. In the CS (pg 22, Section 1.3), the justifications for inclusion of CheckMate 010 and CheckMate 003 was to provide supportive long term survival data (4 years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab.

Table 1. List of relevant RCTs and non-RCTs (adapted from CS, Table 8, pg 54 and Table 19, pg 106)

Trial name (NCT number)	Objective	Intervention	Comparator	Primary study reference
CheckMate 025 (NCT01668784)	To compare nivolumab with everolimus in	Nivolumab 3mg/kg IV every two weeks	Everolimus 10mg orally every day	Motzer *et al*. 2015[37]

Figure 1. Kaplan Meier curves for OS and PFS in Checkmate 010, all randomised patients



Abbreviations in figure: CI, confidence interval; OS, overall survival
Source: Motzer *et al.* 2015[65]

Median OS in advanced RCC patients in CheckMate 003[66] was 22.4 months in patients receiving nivolumab 1 or 10 mg/kg, and survival rate was 71% at 1 year, 48% at 2 years, and 44% at 3 years (**Error! Reference source not found.**).

In CheckMate 003[66], ORR was observed in 29% (10/34) of advanced RCC patients treated with either nivolumab 1 mg/kg or 10 mg/kg; an additional 27% (9/34) of patients experienced stable disease lasting 24 weeks, and 10 out of 34 patients achieved complete or partial response at median duration of 12.9 months (range: 8.4 to 29.1+ months).

4.3.4 HRQoL

In Checkmate 025,[37, 39] HRQoL was assessed using the FKSI-DRS and EQ-5D instruments. The median FKSI-DRS score at baseline was 31.0 during the first year in both treatment groups. Thereafter there was significant improvement in HRQoL in the nivolumab group compared with the everolimus group. In addition, a higher proportion of patients in the nivolumab group (55%) experienced meaningful improvement in FKSI-DRS (defined as ≥2-point increase) compared with 37% of patients in the everolimus group (p<0.001).

Table 2. FKSI-DRS completion rate and median change from baseline in CheckMate 025 (reproduced from CS, pg 78, Section 4.7, Table 14)

Visit	Nivolumab (n=406)		Everolimus (n=397)		*P*-value[a]
	Completion rate, %	Median CFB (range)	Completion rate, %	Median CFB (range)	
Baseline	89	-	86	-	-
Week 4	87	0 (-13.0-11.0)	85	-1.0 (-20.0019.0)	<0.001
Week 8	87	0.0 (-13.0–14.0)	85	-1.0 (-19.0016.0)	<0.001
Week 12	85	0.0 (-19.0-17.0)	89	-1.0 (-18.0-19.0)	<0.001
Week 16	86	0.0 (-16.0-13.0)	89	-1.0 (-17.0-16.0)	<0.001
Week 20	86	0.0 (-11.0-16.0)	89	-1.0 (-16.0-16.0)	<0.001
Week 24	86	0.0 (-10.0-15.0)	87	-1.0 (-13.0-16.)	<0.001
Week 28	86	0.0 (-9.0-12.0)	88	-1.0 (-13.0-14.0)	<0.001
Week 32	88	1.0 (-9.0-15.0)	81	-1.0 (-11.0-15.0)	<0.001
Week 36	84	1.0 (-15.0-18.0)	85	-1.0 (-11.0-15.0	<0.001
Week 40	83	1.0 (-11.0-11.0)	84	-1.0 (-12.0-20.0)	<0.001
Week 44	83	1.0 (-11.0-16.0)	79	-1.0 (-10.0-18.0)	<0.001
Week 48	84	1.0 (-9.0-17.0)	81	-1.0 (-12.0-25.0)	<0.001
Week 52	80	1.0 (-9.0-17.0)	81	0.0 (-10.0-20.0)	<0.001
Week 56	81	1.0 (-7.0-17.0)	80	-1.0 (-17.0-17.0)	<0.001
Week 60	84	1.0 (-10.0-17.0)	79	-1.0 (-10.0-20.0)	<0.001
Week 64	78	1.0 (-9.0-16.0)	76	-1.0 (-8.0-12.0)	<0.001
Week 68	77	2.0 (-7.0-18.0)	73	-1.0 (-10.0-22.0)	<0.001
Week 72	76	1.0 (-6.0-16.0)	71	0.0 (-10.0-9.0)	0.001
Week 76	77	1.0 (-9.0-16.0)	76	0.0 (-10.0-19.0)	0.011
Week 80	76	2.0 (-5.0-11.0)	73	-1.0 (-10.0-25.0)	0.003
Week 84	74	1.5 (-6.0-16.0)	75	0.0 (-15.0-24.0)	0.002
Week 88	80	2.0 (-6.0-16.0)	65	0.0 (-12.0-22.0)	0.005
Week 92	71	3.0 (-4.0-18.0)	60	-1.0 (-12.0-21.0)	0.012
Week 96	81	2.0 (-1.0-7.0)	63	-2.5 (-12.0-20.0)	0.003
Week 100	79	3.0 (-2.0-10.0)	64	-3.0 (-12.0-12.0)	0.002

4.3.6 Adverse events

The company's summary of product characteristics (SmPC) (CS, Appendix 1, pg, 3-37) states, "Nivolumab is associated with immune-related adverse reactions. Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of nivolumab therapy". The SmPC also advises that nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life threatening immune-related adverse reaction. The CS (pg 121–2, Section 4.12, Table 25) reports the incidence of select AEs (defined as AEs with potential immunological cause that is of special clinical interest with the use of nivolumab) in CheckMate 025.[37, 39] In the nivolumab group, reported select AEs with ≥15% incidence were skin (37.2%), gastrointestinal (GI) (24.4%), renal (17.5%) and hepatic (16%), while in the everolimus group they were GI (31.2%), pulmonary (18.6%) and skin (44.6%). However, the majority of the select AEs were transient, hence were readily manageable with either dose interruptions or administration of immune-modulating medications. Table 3 shows a summary of the incidence of select AEs in CheckMate 025.

Table 3. Summary of select AEs reported up to 30 days after last dose in CheckMate 025, all treated patients (reproduced from CS, pg 121, Section 4.12, Table 25)

Event	Nivolumab (n=406)		Everolimus (n=397)	
	All causality	Treatment-related	All causality	Treatment-related
Endocrine	50 (12.3)	39 (9.6)	19 (4.8)	11 (2.8)
Grade 3-4	5 (1.2)	4 (1.0)	3 (0.8)	1 (0.3)
Time to onset, median weeks (range)	16.2 (2.1-91.0)	16.0 (2.1-61.0)	7.6 (3.1-69.3)	5.0 (3.1-40.1)
Resolution rate, n (%)	20 (40.0)	14 (35.9)	11 (57.9)	6 (54.5)
Time to resolution, median weeks (range)	Not reached (0.1-96.1+)	Not reached (1.9-96.1+)	27.9 (0.7-84.6+)	27.9 (0.7-79.4+)
Gastrointestinal	99 (24.4)	51 (12.6)	124 (31.2)	84 (21.2)
Grade 3-4	8 (2.0)	8 (2.0)	6 (1.5)	5 (1.3)
Time to onset, median weeks (range)	10.7 (0.1-83.0)	8.3 (0.1-83.0)	4.4 (0.1-68.1)	3.9 (0.1-64.4)
Resolution rate, n (%)	87 (87.9)	44 (86.3)	99 (81.1)	70 (85.4)
Time to resolution, median weeks (range)	4.1 (0.1-99.9+)	5.6 (0.1-88.3+)	4.9 (0.1-98.1+)	5.3 (0.1-98.1+)
Hepatic	65 (16.0)	46 (11.3)	45 (11.3)	28 (7.1)
Grade 3-4	19 (4.7)	11 (2.7)	4 (1.0)	2 (0.5)
Time to onset, median weeks (range)	8.0 (0.1-88.0)	7.2 (0.1-81.1)	4.4 (0.1-104.0)	4.1 (1.0-38.6)
Resolution rate, n (%)	54 (84.4)	37 (82.2)	32 (71.1)	24 (85.7)
Time to resolution, median weeks (range)	6.7 (0.9+-82.6+)	8.0 (1.6-82.6+)	9.9 (0.7-114.1+)	8.1 (0.9-99.7+)
Pulmonary	23 (5.7)	18 (4.4)	74 (18.6)	70 (17.6)

TRAEs, n (%)	319 (78.6)	349 (87.9)
Grade 3-4 TRAEs, n (%)	76 (19)	145 (37)
All SAEs, n (%)	194 (47.8)	173 (43.6)
TRSAEs, n (%)	47 (11.6)	53 (13.4)
DC due to AEs, n (%)	72 (17.7)	82 (20.7)
DC due to TRAEs, n (%)	31 (7.6)	52 (13.1)
DC due to Grade 3–4 TRAEs, n (%)	19 (4.7)	28 (7.1)
Deaths relating to study drug, n (%)	0	2 (0.5)
Abbreviations in table: AE, adverse event; DC, discontinuation; SAE, serious adverse event; TRAE, treatment related adverse event; TRSAE, treatment related serious adverse event		

In both CheckMate 010 and CheckMate 003 (as in CheckMate 025), the most commonly reported TRAE was fatigue. Reported incidence of fatigue in CheckMate 010[65] was 24% in nivolumab 0.3 mg/kg, 22% in nivolumab 2 mg/kg, and 35% in nivolumab 10 mg/kg groups; while in CheckMate 003, the incidence was 41% in patients with advanced RCC treated with nivolumab (regardless of dose.[65, 66]In addition, discontinuations due to TRAEs were <10% in both CheckMate 010 and CheckMate 003; and most importantly no deaths were reported due to nivolumab toxicity in CheckMate 010 or in advanced RCC patients in CheckMate 003.

4.3.7 Meta-analysis

The company did not perform a meta-analysis as only as single RCT was identified comparing nivolumab with a comparator of interest (i.e. CheckMate 025[37], which compared nivolumab and everolimus). The company therefore conducted a network meta-analysis (NMA) to estimate the comparative efficacy of nivolumab with the other comparators outlined in NICE final scope[23] (i.e. axitinib and BSC).

4.4 Critique of trials identified and included in the indirect comparison and/or network meta-analysis

As a result of the lack of direct evidence for nivolumab compared to axitinib or BSC, as required by the NICE final scope[23], the company conducted a NMA. The ERG is concerned about attempting an NMA using CheckMate 025[37] as the basis for the effectiveness of nivolumab, since proportional hazards do not hold for PFS and for the initial period of OS. Issues with the proportional hazards assumption within CheckMate 025[37] have been discussed previously in Section **Error! Reference source not found.** and Section **Error! Reference source not found.**. This will also be discussed in the summary of the NMA in Section **Error! Reference source not found.**.

4.4.1 NMA methods and assumptions

According to the CS (pg 94-5, Section 4.10.3), the NMA was conducted using the R package 'netmeta'[74] which utilises graph theoretical methods in a frequentist framework to analyse data from

- nivolumab group experienced meaningful improvement in FKSI-DRS compared with the everolimus group (55% vs 37%, respectively; p<0.001);

- Pre-planned subgroup analyses of CheckMate 025 showed statistically significant differences between nivolumab and everolimus treated patients who have had one previous anti-angiogenic therapy (HR 0.71, 95% CI: 0.56, 0.90), MSKCC intermediate (HR 0.76, 95% CI: 0.58 to 0.99) and poor (HR 0.47, 95% CI: 0.30 to 0.73), male (HR 0.73, 95% CI: 0.58 to 0.92) and aged ≥65 to <75 years (HR 0.64, 95% CI: 0.45 to 0.91);

- MSKCC risk group, number of prior anti-angiogenic therapies, age, type and duration of prior therapy, number and site of metastases generally showed greater OS and ORR in the nivolumab group compared with the everolimus group;

- The incidence of select AEs with ≥5% incidence in CheckMate 025 in the nivolumab group were skin (37.2%), GI (24.4%), renal (17.5%) and hepatic (16%), while in the everolimus group they were GI (31.2%), pulmonary (18.6%) and skin (44.6%);

- CheckMate 010,[65] a randomised dose ranging trial and CheckMate 003,[66] a randomised dose escalation trial provided data to support CheckMate 025;

- In the NMA, the ITT analysis of OS indicated that [redacted];

- In the NMA, [redacted]

- The results of the NMA should be interpreted with caution due to the lack of baseline comparability of the included trials (differences and number of prior treatments, and MSKCC risk scores). In addition, there is lack of quality OS RCT data available due to high levels of crossover and/or immaturity of the existing data;

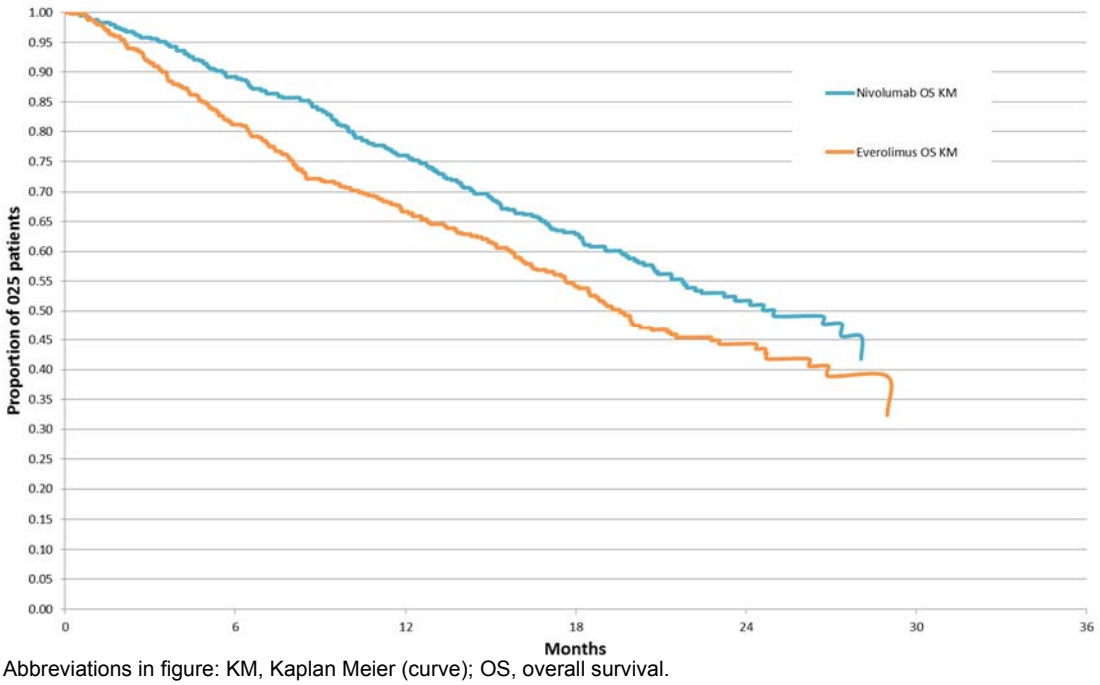
OS, PFS and TTD were analysed independently. The comparison between nivolumab and everolimus was informed by parametric survival analyses of OS, PFS and TTD data from the CheckMate 025 trial.[39] Hazard ratios (HRs) derived from the network meta-analysis (NMA) of PFS and OS, described in Section 0, were applied to the everolimus curve to estimate the proportions of patients in each health state over time for axitinib and best supportive case (BSC) under the assumption of proportional hazards.

The analyses for OS, PFS and TTD are described in Section 0, Section **Error! Reference source not found.** and Section **Error! Reference source not found.**, respectively. The ERG's critique of the company's analyses is included in Section **Error! Reference source not found.**.

5.4.2.1 Overall survival

The Kaplan Meier (KM) curves for the OS observed in the CheckMate 025 trial for the nivolumab and everolimus arms are reported in Figure 2. The number of patients at risk over time in the trial are reported in Table 4.

Figure 2. KM OS data, CheckMate 025 (CS, pg 138, Figure 24)



Abbreviations in figure: KM, Kaplan Meier (curve); OS, overall survival.

Table 4. Number at risk over time, overall survival, CheckMate 025 (CS, pg 138, Table 30)

Months	0	3	6	9	12	15	18	21	24	27	30	33
NAR - Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
NAR - Everolimus	411	366	324	287	265	241	187	115	61	20	2	0
Abbreviations in table: NAR, number at risk.												

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Error! Reference source not found. and **Error! Reference source not found.** summarise the ERG's quality assessment of the company's economic evaluation. **Error! Reference source not found.** summarises the ERG's appraisal of the economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.[23] **Error! Reference source not found.** reports the ERG's appraisal of the company's *de novo* economic models using the Philips checklist.[89]

Table 5. NICE reference case checklist for the base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes.
Perspective costs	NHS and Personal Social Services	Yes. A proportion of the costs in the terminal care health state is reported to be paid by the voluntary sector, but this was shown not to influence the model results.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	No. The company states that there was insufficient time to carry out systematic reviews. The ERG considers this reasonable, as the single technology appraisal (STA) was originally part of a multiple technology appraisal (MTA), and the change did not allow sufficient time for the company to perform a full systematic review.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Not reported in the CS. The company informed the ERG at a later stage that time trade-off was used.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	EQ-5D questionnaires administrated to patients in the CheckMate 025 trial. The sample was not representative of the public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.

acknowledged that the results from the NMA produced results not in line with the expectations of the clinical experts interviewed, as reported in Box 1.

Box 1. Company's comments on the superior efficacy of everolimus over axitinib resulting from the NMA

[…] at clinical review, oncologists did not anticipate a survival advantage of everolimus over axitinib, while recently published evidence suggests similar progression-free survival across axitinib and everolimus in advanced RCC patients previously treated with sunitinib.
Abbreviations in box: RCC, renal cell carcinoma.

The ERG considers the application of the OS NMA HRs to produce implausible results in the economic model based on the clinical experts' consensus on lack of face validity for the comparison between everolimus and axitinib. In addition, the ERG also considers that further modelling and statistical issues remove validity from the company's analysis of both PFS and OS.

To estimate the treatment effectiveness associated to axitinib and best supportive care (BSC), the company applied the HRs estimated from the NMA results, described in Section 0. The crossover-adjusted HRs were selected for the OS; the company stated that this choice was, "in line with NICE DSU TD16" (CS, pg 144, Section 5.3.1). However, the company did not provide further details on the nature and plausibility of the crossover adjustments performed.

The ERG notes that by applying the HRs to estimate and extrapolate relative treatment effectiveness, the company implied that:

1. The hazards between everolimus, axitinib and BSC treatments are assumed proportional; however, they are not proportional between nivolumab and the other comparators (as modelled using non-PH models for both OS and PFS);

2. The relative effectiveness between treatments (i.e. HRs) are assumed constant over the entire time horizon between everolimus, axitinib and BSC. This implication is associated with substantial uncertainty. This should have been explored assuming, for example, declining relative effectiveness over time;

3. PFS and OS associated to axitinib and BSC are not expected to follow the same survival function as everolimus because the HRs were applied to non-PH models. The resulting curves might be not comparable.

influential when compared to differences between treatments in terms of drug acquisition and administration costs and efficacy profiles.

The ERG identified a discrepancy between the reported number of patients in the everolimus group who experienced Grade III/IV pneumonia in the CheckMate 025 CSR, and the number of patients reported in the model. One patient who experienced Grade V pneumonia was included in the model despite the company reporting that only patients with Grade III/IV events were included in the economic analysis. The ERG notes that this minor discrepancy had no impact on the results, and that considering the event was appropriate.[39]

5.5.7 Health-related quality of life

5.5.7.1 EQ-5D data analysis

The HSUVs in the model for PFS and PPS were based on EQ-5D data collected from two trials; CheckMate 025 for nivolumab and everolimus, and the AXIS trial for axitinib and BSC.[79]

The data collected in CheckMate 025 were analysed by the company using a linear mixed model with fixed covariates for the effects of progression status, treatment allocation, and the interaction between treatment arm and progression status and with a random effect for subject. The ERG notes that the company provided the EQ-5D questionnaire completion rates in Section 5.4.1 of the CS, and additional descriptive statistics in Appendix 6 of the CS. However, no details of goodness of fit tests for the statistical model were provided in the CS. Some details on the relative goodness of fit of the selected model compared to a very limited set of alternatives were provided at the clarification stage.

The ERG notes that the company did not provide any justification for the inclusion of an interactive effect between treatment allocation and disease progression status in the HRQoL model, despite this being a non-statistically significant parameter (p=0.654), as shown in **Error! Reference source not found.**. The company only stated that, "For post-progressive patients, clinicians reported that higher utility is expected for nivolumab patients, due to both (i) treatment continuing beyond progression in many cases, and (ii) the immune-response mechanism of nivolumab that implies benefit beyond RECIST-defined progression and beyond treatment continuation" (CS, pg 165, Section 5.4.1).

In the ERG's opinion, even though some patients might experience clinical benefit beyond RECIST-defined progression, a prolonged time on treatment would increase the effects of treatment-related

PMB questions

Q1) Please provide a new analysis in which the utility values for patients having axitinib and everolimus are taken from the axitinib arm of the AXIS trial. The incremental gain in utility for nivolumab vs everolimus should be taken from the CheckMate 025 trial.

R) The analysis requested is presented in Table 2 below while the utility values used in the company, ERG and new analysis are presented in Table 1.

Table 1. Company and ERG results with updated utility assumption

Health state	Company model	ERG analysis	Additional analysis for ACM
PFS, Nivolumab	0.80	0.80	0.73
PPS, Nivolumab	0.73	0.73	0.64
PFS, Everolimus	0.76	0.76	0.69
PPS, Everolimus	0.70	0.70	0.61
PFS, Axitinib	0.69	0.76	0.69
PPS, Axitinib	0.61	0.70	0.61
PFS, BSC	0.69	0.76	0.69
PPS, BSC	0.61	0.70	0.61

Abbreviations in table: ACM, Appraisal Committee meeting; BSC, best supportive care; ERG, evidence review group; PFS, progression-free survival; PPS, post-progression survival.

Table 2. Company and ERG results with updated utility assumption

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case					
Nivolumab	£91,353	2.07			
Axitinib	£46,134	1.25	£45,219	0.82	£55,240
Everolimus	£38,920	1.49	£52,432	0.57	£91,797
BSC	£10,525	0.88	£80,828	1.18	£68,211
Company's base case with ERG corrections					
Nivolumab	£91,326	2.05			
Axitinib	£46,113	1.25	£45,213	0.80	£56,315
Everolimus	£38,933	1.49	£52,393	0.56	£94,320
BSC	£10,525	0.88	£80,801	1.17	£69,106
ERG's preferred ICER *					
Nivolumab	£89.951	2.05			
Axitinib	£44,859	1.49	£45,092	0.56	£81,176
Everolimus	£33,997	1.49	£55,954	0.56	£100,730
BSC	£10,525	0.88	£79,426	1.17	£67,930
Alternative scenario using a generalised gamma model for TTD					
Nivolumab	£94,552	2.05			
Axitinib	£44,859	1.49	£49,693	0.56	£89,459
Everolimus	£36,094	1.49	£58,458	0.56	£105,239

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
BSC	£10,525	0.88	£84,026	1.17	£71,865

Abbreviations in table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost effectiveness ratio; Inc., incremental; QALY, quality adjusted life year; TTD, time to (treatment) discontinuation.

*With all the changes incorporated as in the ERG report, additionally assuming same health state utility values for everolimus, axitinib and BSC taken from Axis trial and assuming the same incremental gain in utility for nivolumab compared with everolimus as in the CheckMate 025 trial.

[Analyses including the confidential patient access scheme for axitinib are in a confidential appendix.]

Q2) Please provide more information about how time is 'discretised' in the model (that is, right vs left Riemann sum). Are any patients assumed to be dead at time zero?

R) Yes, some patients are assumed to be dead at the beginning of the first cycle and do not accrue QALYs or costs. The company's approach therefore underestimates both costs and health benefits of all interventions. However, it must be noted that the more common left-direction approach results in an overestimation of those quantities and leads to a comparable bias, as some patients are considered alive when they are dead. The magnitude of the approximation is dependent on the cycle length; as we deem the cycle length to be sufficiently short, we do not consider this modelling choice to be of any influence on the model results.

Q3) Please provide more information about the subsequent treatments in CheckMate 025 and comment on whether there are imbalances between trial arms. Please also tell us if these treatments are used in the NHS and if they extend survival.

R) The proportion of patient who went on to receive subsequent therapies in CheckMate 025 (as reported by the company) are presented in Table 4. All therapies are available in the UK with the exception of bevacizumab (removed from the analysis by the company). There are no NICE- of CDF-approved third-line treatment options for RCC in the UK (with the exception of everolimus in very rare cases). Furthermore, our clinical experts have advised that treatments received after second-line therapy are unlikely to extend patients' survival, compared with BSC.

The type of subsequent therapy received by patients do not seem to vary greatly between treatment arms, with the exception of subsequent everolimus, which (as expected) was given to fewer patients in the everolimus than in the nivolumab treatment arms. The proportion of patients receiving axitinib as a subsequent therapy is about 12% higher in the everolimus arm than in the nivolumab arm.

Table 4. Proportion of patients receiving subsequent therapies in CheckMate 025 (Table 55 in the CS)

Subsequent treatment	From	
To	Nivolumab	Everolimus
Axitinib	24.15%	36.25%
Bevacizumab	3.17%	5.35%
Everolimus	25.61%	5.60%
Pazopanib	9.02%	15.57%
Sorafenib	6.34%	9.25%
Sunitinib	6.83%	8.27%
Total	**75.12%**	**80.29%**

Note: Totals do not sum to 100%; not all patients progressed to further therapy

[Question 4 relates to the confidential patient access scheme for axitinib; the details are in a confidential appendix.]

Q5) On page 106 you explain that log-logistic and generalised gamma models rely on the AFT assumption, and note that you tested the AFT assumption and found that it did not hold, based on the QQ plot in figure 41. However, on the following page, you reference the QQ plot and say that it did not show a substantial departure from linearity so the use of log-logistic and generalised gamma models are therefore appropriate. Please could you state clearly whether the parametric curves used for OS were appropriate or not?

R) We consider the AFT assumption to be reasonable. However, the degree of departure from linearity observed needs to be noted, as it indicates that alternative models might be suitable. We acknowledge that the conclusion is unclear, and in particular that the sentence, “In the ERG’s interpretation, the QQ plot seems to show a departure from the AFT assumption over the time considered horizon (up to the 55th percentile)”, could have been more clearly phrased.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

You are asked to check the ERG report from BMJ Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE the end of 18 May using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Section 4.5 ERG considering NMA flawed

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 59): "The ERG considers that the company's NMA may be fundamentally flawed and producing biased estimates of treatment effects."	We kindly request this statement is removed on the grounds of factual inaccuracy. It is the paucity of evidence that makes addressing the decision problem a challenge, and not that the NMA methodology is fundamentally flawed.	Section 4.10 of the company submission clearly demonstrated the paucity of comparative evidence available for axitinib and BSC versus nivolumab in this patient group. The NMA analysis undertaken is in line with NICE recommended methodology in the NICE DSU guidelines. Each of the points ascertaining to this point are addressed in further detail in Issues 2-8. In light of these arguments, the paragraph does not provide a balanced representation of evidence presented and is therefore extremely misleading to the reader.	The ERG does not consider the statement to be factually incorrect.

Issue 2 Section 4.4.3 Crossover adjusted NMA: Use of crossover adjusted hazard ratio for the RECORD-1 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 55): "The ERG notes that crossover adjusted estimates have been provided for RECORD-1[77] and TARGET[58]. However, the methodology employed to estimate the "crossover adjusted/free" results has not been assessed by the company	Please amend this section to acknowledge that the NICE single technology appraisal for everolimus, for which the main evidence was the RECORD-1 trial, evaluated the cost effectiveness of everolimus based on the estimates generated using the RPSFT methodology. (https://www.nice.org.uk/guidance/ta219; page 30). Furthermore, please acknowledge that the sponsor would not have access to the individual patient level data for RECORD-1 to assess the suitability of the	The sponsor would not have access to the individual patient level data for the RECORD-1 trial to assess the suitability of the RPSFTM methodology as applied to RECORD-1. As such, the sponsor has deemed previous acceptance of the RPSFTM methodology as applied to RECORD-1 by a NICE	The ERG does not consider the statement to be factually incorrect.

as to whether it is/isn't an appropriate methodology to employ. The ERG considers it likely that the company has made use of published data without carrying out this level of scrutiny."	RPSFTM methodology as applied to RECORD-1.	technology appraisal committee as justification for its use. This is currently outlined in Section 4.10.7 (page 104) of the submission.	

Issue 3 Section 4.4.3 AXIS: Confounding of overall survival by subsequent active treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 55): "Of particular concern are the results used from AXIS[45]; when Motzer et al. report the overall survival results they highlight that, "Analysis of overall survival might have been confounded by subsequent active treatments, which were given to the majority of patients who discontinued study treatment". [45] Given the company's concerns around the impact of crossover, and its use of crossover adjusted/free results for RECORD-1[77] and TARGET[58], the ERG does not understand why the issue of subsequent active treatments in AXIS was not mentioned and accounted for in the CS."	Please amend this section to clearly differentiate between the protocol permitted switch from control to intervention in the RECORD-1 and TARGET trials - crossover - and the use of different subsequent therapies in the AXIS trial, which were not pre-specified in the protocol. The use of subsequent therapies is standard practice in clinical trials and patients in CheckMate 025 also received subsequent treatment. As such, and in addition, please amend this section to acknowledge that the type and pattern of subsequent treatment received in AXIS is that which may be seen in clinical practice and hence that it might not be appropriate to adjust overall survival of AXIS for subsequent treatments received. Furthermore, please amend this	The RECORD-1 and TARGET trials permitted patients to crossover from control (placebo in both cases) to intervention (everolimus and sorafenib, respectively). TARGET permitted crossover from placebo to sorafenib following a statistically significant PFS benefit being observed (May 2005); patients were permitted to crossover prior to disease progression. Patients in RECORD-1 were permitted to crossover upon disease progression. The AXIS trial does not permit patients to crossover from control (sorafenib) to intervention (axitinib). Instead, following discontinuation of the study drug in the AXIS study, patients (54% in the axitinib arm and 57% in the sorafenib arm that were eligible for subsequent therapy) went on to receive subsequent systemic therapy according to the treatment pathway of normal clinical practice. There were no major differences in the type of subsequent therapy received in both arms. Patients in both arms of the AXIS study received mTOR inhibitors and further VEGF/VEGFr	The ERG does not consider the statement to be factually incorrect.

	section to acknowledge that the sponsor would not have access to the individual patient level data for AXIS to perform adjustments to account for subsequent treatments and that such analyses, to our knowledge, have not been published.	inhibitors in balanced measure. The details of which specific drugs were used as subsequent therapy has not been published. In the same light, in CheckMate 025, 55% of patients in nivolumab arm and 63% of patients in everolimus arm went on to receive subsequent therapy. The use of subsequent therapy is present for all studies in this treatment network; subjects will resume the clinical treatment pathway following study participation. Therefore, due to the use of subsequent therapies for all trials in the network (including Checkmate-025) using an unadjusted hazard ratio for the AXIS trial is not expected to bias the results of the NMA in favour of nivolumab. The sponsor would not have access to the individual patient level data for AXIS to perform any type of further analysis.	

Issue 4 Section 4.4.3 Crossover adjusted NMA: Use of unbiased hazard ratio from TARGET trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 55): "The ERG is also concerned about the immature OS results used from TARGET. (58) The company states (CS, page 96, Section 4.10.4), "The TARGET trial permitted crossover from	Please amend this section to highlight that the hazard ratio utilised in the crossover adjusted/free analysis is the only available estimator of treatment effect that is unbiased, free from the confounding effects of patients crossing over from placebo to sorafenib. Furthermore, please amend this	The current text does not acknowledge the merits of the hazard ratio currently utilised in the NMA; i.e. the hazard ratio is derived prior to crossover from placebo to sorafenib being permitted. As such, the currently utilised hazard ratio is the only available estimator of treatment effect that is unbiased, free from the confounding effects of patients crossing over from placebo to	The ERG does not consider the statement to be factually incorrect.

placebo to sorafenib following a statistically significant PFS being observed. Although, at this point, the OS data were relatively immature (220 deaths; 41% of the protocol defined 540 deaths had been observed), the estimation of survival was unbiased and there was a numerical advantage of sorafenib over placebo (HR 0.72, 95% CI: 0.54 to 0.94; p=0.02)". The impact of using immature survival on the results of the NMA will be discussed further in Section 4.4.5."	section to highlight that although the hazard ratio utilised is derived using a dataset with fewer events, it is nominally statistically significant (p=0.02; although not considered statistically significant according to the O'Brien–Fleming threshold used to account for multiple testing) and, therefore, not immature by standard conventions.	sorafenib. Although the hazard ratio utilised is less mature than later available data extractions, it is still nominally statistically significant (p=0.02) – although not considered statistically significant according to the O'Brien–Fleming threshold used to account for multiple testing. As explained in detail in Issue 6, the hazard ratio utilised demonstrates the greatest overall survival benefit of sorafenib compared to placebo.	

Issue 5 Section 4.4.5 AXIS: Adjusting for subsequent treatments in the AXIS trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 60, 2nd bullet): "OS adjustments for crossover – the lack of accounting (or even acknowledging) the impact of subsequent active treatments in AXIS is highly likely to bias the estimated treatment effect for OS. In the presence of crossover, differences in OS are likely to be	Please amend this section to acknowledge that the type and pattern of subsequent treatment received in the AXIS trial was comparable between trial arms and is that which may be seen in clinical practice, and hence, it might not be appropriate to adjust overall survival of AXIS for subsequent treatments received. Furthermore, please amend this section to acknowledge that the	As justified in detail under Issue 3, the AXIS trial does not permit patients to crossover from control (sorafenib) to intervention (axitinib). Instead, patients have received subsequent treatments as is typical in clinical practice. As such, it might not be appropriate to adjust overall survival of AXIS for subsequent treatments because this would occur in clinical practice. The sponsor would not have access to the individual patient level data for AXIS to perform	The ERG does not consider the statement to be factually incorrect.

minimised."	sponsor would not have access to the individual patient level data for AXIS to perform adjustments to account for subsequent treatments and that such analyses, to our knowledge, have not been published.	any type of further analysis.	

Issue 6 Section 4.4.5 Crossover adjusted NMA: Underestimating the benefit of sorafenib over placebo and use of unbiased HR for TARGET trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 60, 3rd bullet): "Immature OS for TARGET – if it is assumed that sorafenib is likely to be more effective than placebo; utilising immature survival data is likely to underestimate the benefit of sorafenib over placebo. While the ERG appreciates that the company was attempting to use crossover free results, the likely impact of this should have been explicitly stated as a limitation and the potential direction of bias acknowledged."	Please amend this section to remove the reference to underestimating the benefit of sorafenib over placebo. Please amend this section to remove the reference to bias and instead refer to uncertainty.	The hazard ratio used in the crossover free NMA for the TARGET trial (0.72 [95% CI; 0.54, 0.94]: May 2005) demonstrates the greatest overall survival benefit of sorafenib compared to placebo available from the two primary publications. (Escudier et al. 2007 and Escudier et al. 2009). All other hazard ratios, are greater than 0.72 and therefore demonstrate a smaller benefit of sorafenib over placebo. The following are a summary of all other available hazard ratios from the two clinical trials: • 0.77 [95% CI; 0.63, 0.95; p=0.015] (Nov 2005) • 0.88 [95% CI; 0.74,1.04; p=0.146] (Sep 2006) • 0.78 [95% CI; 0.62, 0.97; p=0.0287] (Sep 2006; censoring for crossover; NICE DSU TSD 16 states that this approach is prone to selection bias through informative censoring) Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007; 356(2):125-34.	The ERG does not consider the statement to be factually incorrect.

		Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009; 27(20):3312-8. In relation to the reference to bias, the currently utilised hazard ratio is the only available estimator of treatment effect that is unbiased, free from the confounding effects of crossover from placebo to sorafenib. However, due to the immaturity of the data, this estimate is subject to the most uncertainty, although still nominally statistically significant, p=0.02.	

Issue 7 Section 4.4.5 Crossover adjusted NMA: Minimising any relative benefit for axitinib compared to sorafenib in the network

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 60, 4th bullet): "The impact of not adjusting for subsequent active treatments in AXIS and not using mature and crossover-free OS data for TARGET is likely to minimise any relative benefit for axitinib compared to sorafenib in the network."	Please amend this section to acknowledge that mature and crossover-free OS data for TARGET do not exist and that the type and pattern of subsequent treatment received in the AXIS trial is that which may be seen in clinical practice, and hence, it might not be appropriate to adjust overall survival of AXIS for subsequent treatments received (see issue 3 for further description). Furthermore, please amend this section	As the sponsor, it is not possible to access the individual patient level data for the AXIS trial to make this assessment independently. As described previously (Issue 6), the hazard ratios utilised for the TARGET trial in the crossover free NMA (0.72 [95% CI; 0.54, 0.94]: May 2005) demonstrate the greatest overall survival benefit of sorafenib compared to placebo available from the two primary publications. (Escudier et al. 2007 and Escudier et al. 2009) and is not biased by patients crossing over from placebo to	The ERG does not consider the statement to be factually incorrect.

	to acknowledge that the sponsor would not have access to the individual patient level data for the AXIS trial to perform adjustments to account for subsequent treatments received in AXIS . Finally, please remove the reference to the TARGET trial minimising any relative benefit for axitinib compared to sorafenib in the treatment network (see issue 6 for further justification).	sorafenib.	

Issue 8 Section 4.4.5 NMA: Differences in prior treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 60, 5th bullet): "Differences in prior treatment – while the ERG is unable to assess the impact of differences in prior treatments, it seems likely that this will make a difference in the estimated PFS and OS for trials included in the network."	Please acknowledge that the NMA is conducted using relative treatment effects (log-hazard ratios). As such, although absolute effects in OS and PFS might vary according to treatment history, the NMA results would only be invalidated if the relative treatment effects (log-hazard ratios) varied across levels of these subgroups. As such, please amend this section to highlight that subgroup analyses in CheckMate 025 demonstrated a consistent OS benefit with nivolumab irrespective of prior treatment history (i.e. 1 vs 2 prior anti-angiogenic agents and type of prior therapy ,sunitinib vs pazopanib).	Subgroup data for the CheckMate-025 trial are presented on page 80 (Figure 14) of the CS. The ERG report acknowledges (page 54, text above Table 19) that the number of lines of previous therapy may have limited impact on the network since the subgroup analysis of OS in CheckMate 025 shows no statistically significant difference in treatment effect between patients who have had one or two previous therapies. Similarly, the CS (page 80, Figure 14) shows consistency in relative treatment effects across type of prior therapy (sunitinib vs pazopanib).	The ERG does not consider the statement to be factually incorrect.

	Furthermore, for the AXIS trial, hazard ratios utilized were those derived for the subgroup of patients previously treated with an anti-angiogenic therapy, sunitinib. This is representative of the current clinical treatment pathway in England. The influence of prior therapy with only cytokine therapy was thus eliminated.	To provide a comparison of nivolumab to axitinib within the most comparable patient population, the HR utilised for the AXIS trial was that derived for the subgroup of patients previously treated with sunitinib (page 98 of CS).	

Issue 9 Sections 1.2 and 4.5 OS NMA results: Upper confidence interval limit for comparison of nivolumab to axitinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 3 and 62): "In the NMA, the ITT analysis of OS indicated that nivolumab had .....but not versus axitinib ([redacted])."	There is a typo in the upper confidence interval for the comparison of nivolumab to axitinib for OS. The text should read: "In the NMA, the ITT analysis of OS indicated that nivolumab had .....but not versus axitinib ([redacted])."	Typographical error.	The ERG notes that the pages that the company is referring to are page 3 and 63 in the ERG's version of the report. The ERG thanks the company for highlighting the factual error. The proposed amendment has been made.

Issue 10 Sections 5.5.7 and 6.3 Justification of ERG base case HSUV assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 119, ERG report, the ERG state the following: "*The ERG's clinical experts stated that the difference in both pre-and post-progression survival utility values between everolimus*	We request that the ERG verify that the ERG base case utility assumptions are in line with the	ERG base case utility assumptions are not in line with the clinical opinion from the company's clinical experts. From the ERG report, it is not clear that ERG base case utility assumptions are consistent with the opinion of the ERG's clinical experts.	The ERG does not consider these statements to be factually incorrect.

and axitinib is implausible, and is likely to be a reflection of the different baseline characteristics of patients in the trials, as already noted in Section 5.5.3. *The company assumed that the HRQoL of patients receiving BSC was comparable to that of patients receiving axitinib; this was justified by the fact that the toxicity experienced when taking axitinib offsets the benefits of treatment. The assumption is deemed reasonable by the ERG in light of the clinical experts' feedback and in line with the assumptions in TA333"* This informs the ERG base case utility assumptions (p141): "*The ERG's base case included changes in the following assumptions: …..* *4. Assuming the same HSUVs for axitinib and BSC as the values set for everolimus and estimated from the CheckMate 025 trial, in line with clinical expert opinion;*"	opinions of the ERG's clinical experts.	It cannot be deduced from the ERG report that assuming the same HSUVs for axitinib and BSC as the values set for everolimus and estimated from the CheckMate 025 trial is in line with ERG clinicians' expert opinion. With reference to Issue 12, it is possible that clinical experts doubt the plausibility of the scale of difference between axitinib and everolimus utility estimates inferred across AXIS and CheckMate 025 trials, without supporting the assumption that axitinib patient utility is best characterised by data from CheckMate 025 everolimus patients. As described in the company submission (pages 167-168) and company response to clarification question B3, the tolerability profile of axitinib, along with the clinical tendency to treat axitinib patients with the highest possible dose they can tolerate (i.e. treat until a toxicity reaction) (page 120, ERG report), suggest an unfavourable patient experience on axitinib. The ERG assumption that axitinib HSUVs should be set equal to CheckMate 025 everolimus HSUVs appears to be unjustified and not validated by clinical opinion. The ERG's conclusion that the most appropriate assumption for BSC patient utility is to assume it is equal to that reported by CheckMate 025 everolimus patients is not in line with evidence from the literature and from the company's clinical experts about the drivers of utility for these patients. It is not clear from the report that this assumption reflects the opinion of the ERG's clinical experts.	

Issue 11 Sections 5.5.8 and 6.3 Justification of rejection of CheckMate 025 dose intensity estimates for ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 121, ERG report, the ERG state the following: "*the ERG is uncertain whether the dose reduction factors applied to the three active treatments are appropriate and comparable. The assumptions associated with the highest uncertainty are the removal of the delayed doses from the nivolumab acquisition costs and the assumption of a constant reduction (or increase) in the doses over time*." On page 141 of the ERG report: "*The ERG's base case included changes in the following assumptions: …..* *3. Assuming patients would receive the entire planned doses of nivolumab and everolimus*." On page 147 of the ERG report: "*The ERG considers that the calculations for the planned doses received were not sufficiently clear, and that the company did not justify the assumption of a constant reduction in the quantity of drug used over time*."	We kindly request that the ERG clarifies its justification for their amendment to base case assumptions regarding dose intensity.	It is not clear how the ERG have arrived to 100% dose intensity as the most plausible assumption for nivolumab administration in NHS practice. It is highly unlikely that 100% of scheduled doses will be administered for intravenous drugs, and particularly important to accurately reflect this in the model using the best available data (CheckMate 025). As reported in Section 5.5.2 of the CS, 5.075% of doses were delayed for an average of 14 days. Given time-to-discontinuation (TTD) data informed treatment duration assumptions, and nivolumab is administered fortnightly, it is not clear how further evidence is needed to indicate that these delayed doses should be accounted for as presented in the CS. Nivolumab would not be administered earlier than two weeks after a delayed dose, and delayed doses would not be reflected in TTD data. Similarly, CheckMate 025 data are the best source for assumptions regarding omitted doses in clinical practice. Assuming no omitted doses for an intravenous treatment is less valid than using data from CheckMate 025, which showed 2.5% of doses were omitted. The assumption of constant dose reductions over time is a useful simplification, not an assumption that introduces bias, and not a valid reason for using	The ERG does not consider this to be a factual error.

		implausible assumptions instead.	

Issue 12 Section 5.5.3 Potential misinterpretation of clinical expert opinion

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 102, ERG report, the ERG state the following: "*The ERG notes that the uncertainty associated with the assumption of homogeneity between the two populations would propagate to the cost-effectiveness analysis results. Treatment effectiveness estimates used in the model were based on a network meta-analysis combining the two populations. As for HRQoL, estimates were based on EQ-5D data collected in the respective trials and were used in the model without adjustments. As reported in Section 5.4.4 and Section 5.5.7.2, the HSUVs for patients receiving everolimus and axitinib were substantially different. According to the ERG's clinical experts, this difference is most likely a result of the differences between the two populations, and not due to treatment.*"	We are concerned with Section 5.5.3 of the ERG report as a whole, with reference to the ERG's reporting of the ERG's clinical expert's opinions, addressed in Issue 11. The last sentence of the paragraph prompts a further query over the ERG's interpretation of clinical opinion. Although the ERG clinical experts may have felt that the differences may be due to differences between the two populations, it does not follow that they also believed there were no differences anticipated due to treatment.	Potential misinterpretation of clinical expert opinion.	The ERG does not consider this to be a factual error.

Issue 13 Section 5.5.1 Inconsistent reporting of ERG clinicians' opinions

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Pages 96-97, Table 49, column 3, row 15, ERG report, the ERG state the following: "*The baseline characteristics of patients who enrolled in the CheckMate 025 trial were assumed appropriate for the model population. According to the ERG's clinical experts, the patients in CheckMate 025 trial had a better prognosis than previously treated advanced or metastatic RCC patients encountered in routine clinical practice in the UK*." This, and subsequent statements, contradicts earlier reporting of ERG clinician opinion. An example from Sections 1.1 (page 1) of the ERG report: "*The ERG's clinical experts consider the population in CheckMate 025 to be reflective of patients in English clinical practice. The ERG therefore considers the population in CheckMate 025 to be relevant to the decision problem*." Further examples can be found in Sections 1.4 (page 6) and 3.1 (page 17).	Please clarify ERG clinicians' opinion. Please align this statement, and all similar statements from this point onwards, to reflect statements in earlier Sections (assuming these are true, as this would be in line with documented clinical advice from three oncologists, each currently treating patients with advanced RCC within the NHS in England or Wales and each with some experience of HTA, included in the CS), where it is stated that ERG clinical experts consider the population in CheckMate 025 to be reflective of English clinical practice.	Clarity regarding ERG clinicians' opinion is vital to support conclusions drawn by the ERG. The company and the public cannot from the ERG report assess the ERG's approach to eliciting clinical opinion; it is essential for transparency that reporting is consistent.	The ERG does not consider this to be a factual error.

Issue 14 Section 5.5.4 ERG claims over face validity and plausibility of company network meta-analysis results

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 111-112, ERG report, the ERG state the	We request that the ERG	Section 4.10 of the company	The ERG does not consider

following: "*The clinical opinion sought by the ERG suggested that the comparative OS between axitinib and everolimus estimated by the company lacked face validity. The experts independently agreed on the non-inferiority of axitinib compared to everolimus, both in terms of OS and PFS. The company acknowledged that the results from the NMA produced results not in line with the expectations of the clinical experts interviewed, as reported in Box 10*… *..The ERG considers the application of the OS NMA HRs to produce implausible results in the economic model based on the clinical experts' consensus on lack of face validity for the comparison between everolimus and axitinib. In addition, the ERG also considers that further modelling and statistical issues remove validity from the company's analysis of both PFS and OS*."	ensures claims of implausibility of the company's base case analysis are not made on the basis of clinical agreement of the non-inferiority of axitinib versus everolimus. We request that the lack of evidence over relative treatment effectiveness between axitinib and everolimus, *in terms of overall survival*, is captured in the ERG's claims over face validity.	submission clearly demonstrated the paucity of comparative overall survival evidence for axitinib versus everolimus in this patient group. Axitinib has demonstrated higher overall response rates in key clinical trials but no improvement in progression-free survival. It may follow that clinical experts expect axitinib to perform no worse than everolimus in terms of overall survival. It does not follow that the overall survival network meta-analysis presented by the company is implausible or lacks face validity as it reports a numerical overall survival advantage for everolimus versus axitinib.	this to be a factual error.

Issue 15 Section 1.4 Misrepresentation of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 4, ERG report, the ERG conclude their Summary with the following paragraph: "*The ERG assumed equal effectiveness between everolimus and axitinib based on clinical opinion, as the base case estimates presented by the company were deemed*	We kindly request that this paragraph is removed.	It does not follow that as the ERG's clinical experts stated that axitinib would be at least as effective as everolimus, the ERGs base case results are likely to underestimate the effectiveness associated with axitinib. Arguments presented by the ERG that the most robust and reliable estimates of relative effectiveness, in terms of overall survival at least, are their expert's opinion and not those from the NMA presented in the	The ERG does not consider this to be a factual error.

implausible. As the ERG's clinical experts stated that axitinib would be at least as effective as everolimus, the ERG's base case results are likely to underestimate the effectiveness associated with axitinib. In conclusion, based on the assumptions made in the model and according to clinical expert opinion, the ICER for the comparison between nivolumab and axitinib might have been underestimated."		company's submission (CS), are unconvincing. The NMA synthesises the relevant clinical data following NICE DSU guidelines, as justified in response to Issues 1-8. Clinical opinion on relative overall survival estimates are likely to be associated with considerable (recognised) uncertainty. It is not possible to interpret elicitation methods from the ERG report. In light of these arguments, the paragraph does not provide a balanced representation of evidence. Further, it does not follow that if the effectiveness of axitinib is underestimated, the nivolumab vs axitinib ICER is likely to be underestimated. While the last sentence of the paragraph doesn't explicitly state this, it is implied, which is misleading. In Sections 4.3.1 and 4.5 of the ERG report (pages 40 and 63), the ERG note their clinical experts' opinion that a therapy such as nivolumab's immunotherapeutic mechanism of action may achieve a plateau at a higher survival rate than targeted agents or chemotherapy. This was reflected in documented clinical advice from three oncologists, each currently treating patients with advanced RCC within the NHS in England or Wales and each with some experience of HTA, included in the CS. The base case analyses (CS or ERG) do not account for this anticipated effect, but scenario analyses in the CS illustrated the potential effect upon the nivolumab vs axitinib ICER (reduced from £42,417 to £22,923). There is good reason to suggest the true ICER might have been overestimated, and we ask that the ERG Summary does not conclude on a biased note.	

Issue 16 Section 5.5.7 Misleading claim of results contradicting company's statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 116, ERG report, the ERG state the following in criticism of the approach to EQ-5D data analysis: "*The ERG notes that the company did not provide any justification for the inclusion of an interactive effect between treatment allocation and disease progression status in the HRQoL model, despite this being a non-statistically significant parameter (p=0.654), as shown in Table 50. The company only stated that, "For post-progressive patients, clinicians reported that higher utility is expected for nivolumab patients, due to both (i) treatment continuing beyond progression in many cases, and (ii) the immune-response mechanism of nivolumab that implies benefit beyond RECIST-defined progression and beyond treatment continuation" (CS, pg 165, Section 5.4.1).* *However, the effect included in the model seems to contradict the company's statements, as it indicates that the HRQoL of patients who progressed in the nivolumab arm worsened more than in patients who progressed after treatment with everolimus, coeteris* (sp) *paribus*."	We kindly request the second paragraph is removed on the grounds of factual inaccuracy.	The parameter estimate for the interactional effect does not contradict the company's statements, and the implication is misleading to the reader. As expected, utility decreased for patients on both arms of CheckMate 025 upon RECIST-defined disease progression. However, the higher post-progression utility reported by nivolumab patients versus everolimus patients (0.76 vs 0.70; Table 38, ERG report) reflects our text on page 165 of the company submission. A different utility reduction upon progression across treatment arms would have been conceivable and not contradictory. A smaller reduction for everolimus patients may have been explained by the removal of toxicity effects as (i) everolimus exhibited a less favourable tolerability profile than nivolumab in Checkmate 025 and (ii) for everolimus time to discontinuation was similar to progression-free survival, in contrast to nivolumab.	The ERG notes that the pages that the company is referring to is page 118 in the ERG's version of the report. The ERG thanks the company for pointing this out. The ERG has removed the second paragraph as requested by the company.

Issue 17 Section 5.5.1 Misleading ERG statement about reliability

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Pages 96-97, Table 49, column 3, row 14, ERG report, the ERG state the following: "*The survival analysis that was carried out for the head-to-head trial data for nivolumab and everolimus was extensive and well reported. The ERG notes that the company used the proportionality of the hazards as a decision criterion while performing analyses using regression models which do not make use of the proportional hazard (PH) assumption; furthermore, the accelerated failure time (AFT) or proportional odds (PO) assumptions underlying non-PH models were not explored when assessing the appropriateness of AFT and/or PO models.* *A network meta-analysis (NMA) was carried out to obtain hazard ratios (HRs) for PFS and OS for axitinib and BSC compared with nivolumab. Based on clinical opinion, the ERG disagrees with the assumption that patients in the CheckMate 025 trial and in the AXIS trial are a homogeneous population given the differences at baseline in terms of prognosis and number of previous therapies received.*[37, 90] *The results of the NMA showed everolimus to be more effective than axitinib; this was considered implausible and unexpected by the ERG's and the company's clinical experts.* *Additionally, the ERG notes that there are other theoretical issues regarding the incorporation of the NMA results into the survival results from the CheckMate 025 trial, as detailed in Section 5.5.5. The*	Please remove the last sentence, as in light of the ERG's additional investigations to validate AFT and PH assumptions it is misleading.	Company assumptions regarding PH and AFT were generally validated by the ERG's further investigations, leading the ERG to adopt similar assumptions in their preferred base case. The last sentence is misleading to the reader, as it over-represents the uncertainty around relative treatment effectiveness. Additionally, if Table 49 of the ERG report is solely about good practice within decision analytic modelling, the sentence is misplaced, and could be justifiably removed on these grounds.	The ERG does not consider this statement to be factually incorrect.

ERG does not consider the extrapolations based on the results of the NMA to be reliable."			

Issue 18 Section 6.3 Clinical plausibility of TTD scenario

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 143, ERG report, the ERG state the following: "The ERG presents an alternative scenario using a generalised gamma model for TTD, considered equally as plausible as the base case in which a log-normal curve is selected, based on the relative measures of goodness of fit to the data associated to the two curves."	We kindly request that the ERG clarifies whether any input from clinical experts was sought to validate TTD model selection.	We concur with the ERG's use of goodness-of-fit statistics to inform model selection for TTD, but given the sensitivity of model results to the generalised gamma scenario, clinical validation for extrapolated data becomes important. We have contacted Dr James Larkin, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, to seek advice on plausibility of different TTD assumptions via email. Dr Larkin's advice is that while it is plausible a small number of patients would remain on everolimus treatment after 4 years, he would expect ~1% rather than ~2%, supporting the ERG's base case log-logistic assumption (email communication, 16 May 2016).	The ERG does not consider this to be a factual error.

Issue 19 Section 5.5.5 Supportive evidence for relative treatment effectiveness estimates in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 112, ERG report, the ERG state the following: "*No evidence was presented to support*	We kindly request this text is removed on the grounds of factual	Section 5.7.2 of the company submission compared clinical outcomes from the model to clinical outcomes from key trials, as supportive evidence for different	The ERG notes that the page that the company is referring to is page 114 in the ERG's

the different relative treatment effectiveness between the treatments"	inaccuracy.	relative treatment effectiveness between the treatments.	version of the report. The ERG thanks the company for highlighting this issue. The text has been removed as requested.

Issue 20 Section 5.5.1 ERG criticism of reporting of benefit valuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 95, Table 48, column 3, row 11, ERG report, the ERG state the following: "*Not reported clearly. The company stated that, "The UK EQ-5D tariff was used to value patient questionnaire responses" (CS, pg 161, Section 5.4.1) but did not include references or additional details."*	Please amend cell text to "TTO"	We regret in retrospect not including an appropriate reference (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-3l-value-sets.html (accessed 13 May 2016)), and had hoped that it could have been easily inferred from our level of reporting which tariff had been used. If not, we would have hoped for the ERG to have resolved any uncertainty they had around this with a brief clarification question. We therefore kindly request the proposed amendment.	The ERG notes that the pages that the company is referring to is page 97 in the ERG's version of the report. The ERG thanks the company for the additional information provided at this stage and amended the text for sake of transparency.

Issue 21 Section 5.4.2.1 Reporting of number at risk for CheckMate 025 overall survival in the electronic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page , ERG report, the ERG state the following: "*The ERG notes that the*	We kindly request that this text is removed.	Factual inaccuracy. We believe the ERG are mistaken. The numbers in Table 27 of the ERG report are identical to those in	The ERG agrees with the company and confirms that the values reported in the

*numbers of patients at risk reported by the company in Table 30 of the CS (and replicated in Table 27**Error! Reference source not found.**) did not correspond with the values included in the electronic model (not shown). However, the KM curves in the model were identical to the ones shown in Figure 24 of the CS (replicated in Figure 19).*		sheet "Results", range "B285:N287" of the submitted model, where numbers at risk are reported.	company submission are identical to those reported in the economic model submitted by the company. The text has been removed as per the company's request.

Issue 22 Section 1.3 Description of company's view on appropriateness of standard parametric models to PFS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 4, ERG report, the ERG state the following: "*The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit sufficiently well the data, and explored more flexible models*."	Please amend the text to the following: "*The company did not consider standard parametric models (i.e. exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to fit sufficiently well the PFS data, and explored more flexible models*."	This statement comes directly after reference to OS data, but concerns PFS data. Though a very minor issue, it is easily resolved, and the current text could be misinterpreted by the reader.	The ERG thanks the company for highlighting this issue and amended the text as requested by the company.

Issue 23 Section 4.2.2 Discontinuation rate in CheckMate 010

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (Page 34): "The ERG considers both CheckMate 010[65] and CheckMate 003[66] to be well conducted trials but highlights the high discontinuation rate in CheckMate 010[65] (nivolumab 0.3 mg/kg [50/60], nivolumab 2 mg/kg [49/54] and nivolumab 10 mg/kg [44/54])."	Please reconsider the phrasing of this sentence relating to discontinuations in light of the justification provided.	The discontinuation rate for CheckMate 010 quoted is largely due to progressive disease seen after a minimum follow-up period of 14 months, at the point of data cut-off in May 2013. It is not unexpected to see that, in a previously treated RCC population with analysis done after follow-up of over a year, most patients would have progressed on / discontinued study treatment. Treatment-related AEs leading to discontinuation of study drug occurred in 7% (n = 11 of 167) of patients in CheckMate 010. This is in line with TRAE leading to discontinuation rates seen with nivolumab in the CA025 study- 8% (31 of 406 patients). In CA010, the most common reason for treatment-related discontinuation was an elevated level of serum AST, occurring in two patients.	The ERG does not consider the statement to be factually incorrect.

Issue 24 Section 4.3.1 Clinical effectiveness results: Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report presents the Motzer *et al.* 2015 figure (ERG report Figure 7, page	Please add the Plimack et al. 2015 figure (figure 20 of manufacturer submission) into this section to showcase the longer term	Figure 20 in the manufacturer submission provides longer term OS data for CheckMate 010 than the Motzer *et al.* figure and the	The ERG does not consider the statement to be factually incorrect.

41) for OS for CheckMate 010. In the CS, the Plimack et al. 2015 figure for OS is utilised because this contains the longer term OS data."	OS data from CheckMate 010.	additional OS data is important to show the long-term treatment effect of nivolumab over 4 years rather than 3 years.	

Issue 25 Minor text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The following textual inaccuracies were identified within the ERG report.	• Page 2, page 49: "select adverse events with ≥5% incidence" – this should read ≥15%. • Page 28: "the justifications for inclusion of CheckMate 010 and CheckMate 003 was to provide supportive long term survival data (3 years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab" – this should read "…(**4** years in CheckMate 010 and 5 years in CheckMate 003) for nivolumab" • Page 41: "Figure 7. Kaplan Meier curves for OS and PFS in Checkmate 010, all randomised patients", the source is listed as Motzer et al. 2014 – this should read Motzer et al. **2015**. • Page 45: "median duration of 12.9 months (80% CI: 8.4 to 29.1 months)" – the 80% CI should read 8.4 to 29.1**+** months • Page 51: "discontinuations due to TRAEs were >10%" – this should read **<**10%.	These changes will improve both the accuracy and clarity of the document.	The ERG notes that pages 2, 49, 28, 41, 45, 51, and 62 that the company is referring to are respectively pages 2, 49, 28, 42, 46, 52, and 63 in the ERG's version of the report. The ERG thanks the company for highlighting the factual errors. The proposed amendment has been made.

Issue 26 Academic and commercial in confidence marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
In places, academic in confidence marking has been applied when not needed and vice versa.	• Page 2: "overall survival (OS), defined as the time from randomisation to date of death, was significantly better in the nivolumab group compared with everolimus group (hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.57 to 0.93; p=0.002). Progression-free survival (PFS) was defined as the time from randomisation to first documented RECIST defined progression or death from any cause. Median PFS was not statistically significant between nivolumab (4.6 months, 95% CI: 3.7 to 5.4) and everolimus (4.4 months, 95% CI: 3.7 to 5.5) groups (HR 0.88, 95% CI: 0.75 to 1.03, p=0.11)" is marked up as AIC – this should all be unmarked text. • Page 2: "Investigator-assessed ORR using the RECIST criteria was significantly higher in the nivolumab (25%) compared with the everolimus group (5%) (odds ratio [OR] 5.98; 95% CI: 3.68 to 9.72; p<0.001). The ORR, with a confirmatory scan after ≥4 weeks (that is, confirmed ORR), was also significantly superior (p<0.001) in the nivolumab group (22%) compared with the everolimus group (4%)" is all marked up as AIC – this should all be unmarked text. • Page 2: "more patients in the everolimus group than in the nivolumab group experienced at least one treatment-related adverse event (TRAE) (nivolumab 78.6% vs everolimus 87.9%), grade 3–4 TRAEs (nivolumab 19% vs everolimus 37%) and discontinuations due to TRAEs (nivolumab 7.6% vs everolimus 13.1%)." – this should all be unmarked text. • Page 2-3: "in the nivolumab group were skin (37.2%),	These changes will maintain the correct AIC and/or CIC nature of the data when needed.	The ERG thanks the company for highlighting the factual errors. The proposed amendments have been made.

	gastrointestinal (GI) (24.4%), renal (17.5%) and hepatic (16%), while in the everolimus group they were GIs (31.2%), pulmonary (18.6%) and skin (44.6%)" is all marked up as AIC – only the percentages need to be marked up as AIC. • Page 50: "more patients in the everolimus group experienced at least one treatment-related adverse event (TRAE) (nivolumab [78.6%] vs everolimus [87.9%]), grade 3–4 TRAEs (nivolumab [19%] vs everolimus [37%]) and discontinuations due to TRAEs (nivolumab [7.6%] vs everolimus [13.1%]) compared to the nivolumab group in CheckMate 025" is all marked up as CIC – TRAEs and grade 3-4 TRAEs do not need to be marked up.		