NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

For publication – Redacted

Pre-meeting briefing

Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- 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

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key abbreviations			
AE	Adverse event	MSKCC	Memorial Sloan Kettering Cancer Center
1°	Primary	NE	Not evaluable
2°	Secondary	NIVO+IPI	Nivolumab in combination with ipilimumab
AIC	Akaike information criterion	NMA	Network meta-analysis
BIC	Bayesian information criterion	NR	Not reached
CI	Confidence interval	ORR	Overall response rate
DoR	Duration of response	OS	Overall survival
ECOG	Eastern Cooperative Oncology Group performance status	PD-1	Programmed cell death protein
EoL	End of Life	PD-L1	Programmed death receptor ligand-1
EQ-5D	EuroQol Group 5-Dimensions questionnaire	PFS	Progression-free survival
EQ-5D-3L	EuroQol Group 5-Dimensions 3-levels questionnaire	PH	Proportional hazard
ERG	Evidence Review Group	PPS	Post-progression survival
FACT-G	Functional Assessment of Cancer Therapy-General	QALY	Quality adjusted life years
FKSI-19	National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy – Kidney Symptom Index	RCC	Renal cell carcinoma
HR	Hazard ratio	RCT	Randomised controlled trial
HRQoL	Health-related quality of life	RECIST	Response Evaluation Criteria in Solid Tumours
ICER	Incremental cost effectiveness ratio	SAE	Serious adverse event
IMDC	The International Metastatic Renal Cell Carcinoma Database Consortium	TTD	Time to treatment discontinuation, time to discontinuation
IRRC	Independent radiology review committee	TTR	Time to response
KM	Kaplan-Meier	Tx	Treatment
KPS	Karnofsky performance status	VEGFR-TKI	Vascular endothelial growth factor receptor-tyrosine kinase inhibitor
LYG	Life year(s) gained		

Disease background and management

Kidney cancer

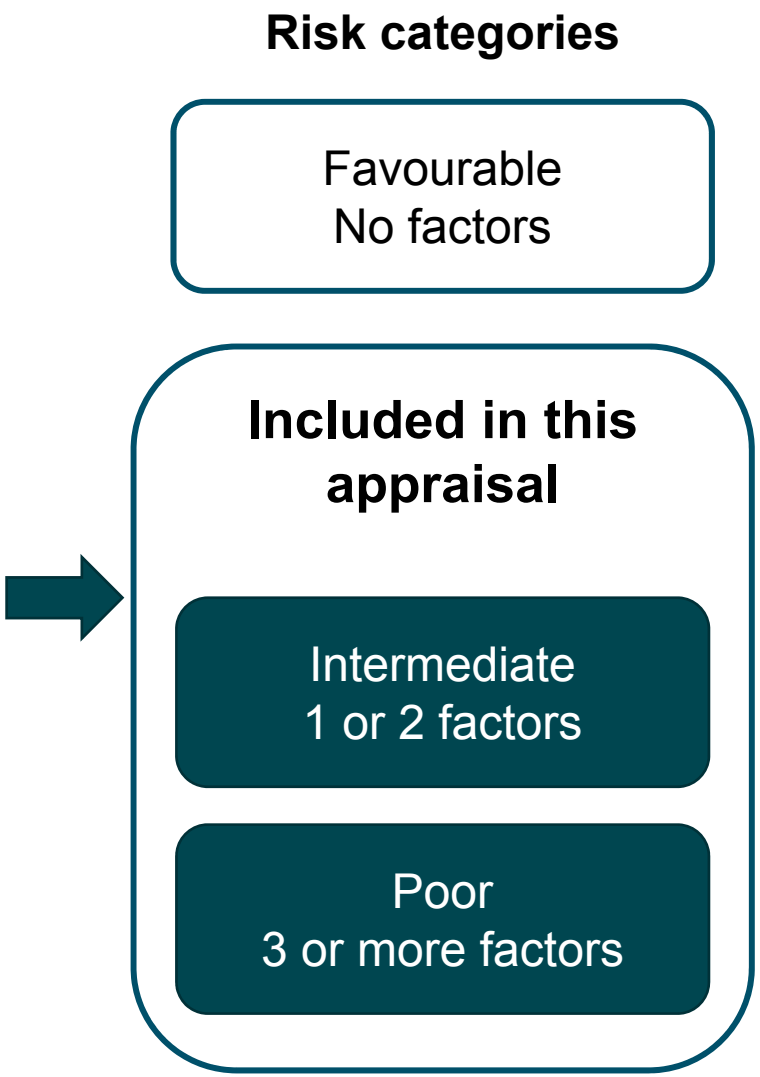
- More common in men than women
- Five-year survival is 56%, varying with age
- 86% of renal cancers are renal cell carcinoma (RCC)

Renal cell carcinoma

- Estimated 9,045 new diagnoses in England per year
- Disease is often locally advanced or metastatic at point of diagnosis
- Early stage disease can be treated surgically – half of patients who have surgical treatment will develop metastatic disease
- Overall survival for people with metastatic disease is 8 months to 3.6 years. The life expectancy of people with RCC is a key issue for committee to consider

IMDC Risk Categories

International Metastatic Renal Cell Carcinoma (IMDC) risk score 2013	
Factor	**Poor prognostic factor**
Karnofsky Performance Status (KPS)	Less than 80%
Time from diagnosis to treatment	Less than 12 months
Anaemia	Haemoglobin below lower limit of normal
Hypercalcemia	Corrected calcium above upper limit of normal
Neutrophilia	Neutrophil count above upper limit of normal
Thrombocytosis	Platelet count greater than upper limit of normal



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Nivolumab plus ipilimumab (Opdivo and Yervoy)
Bristol-Myers Squibb

Marketing authorisation	Nivolumab with ipilimumab (NIVO+IPI) is indicated for the treatment of adult patients with intermediate-/poor-risk advanced renal cell carcinoma
Administration & dose	Intravenous infusion Nivolumab 3 mg/kg + ipilimumab 1mg/kg every 3 weeks for 4 doses. Then nivolumab 3mg/kg every 2 weeks
Mechanism of action	Antibody that specifically binds to anti-programmed cell death-1 (PD-1) receptor on the surface of immune cells and restores T-cell activity by blocking the inhibitory pathway with PD-L1
Cost	List price: Nivolumab 100mg vial = £1,097.00 Ipilimumab 200mg vial = £15,000.00 Average cost per course (at list price): [redacted] Presented analyses incorporate patient access scheme

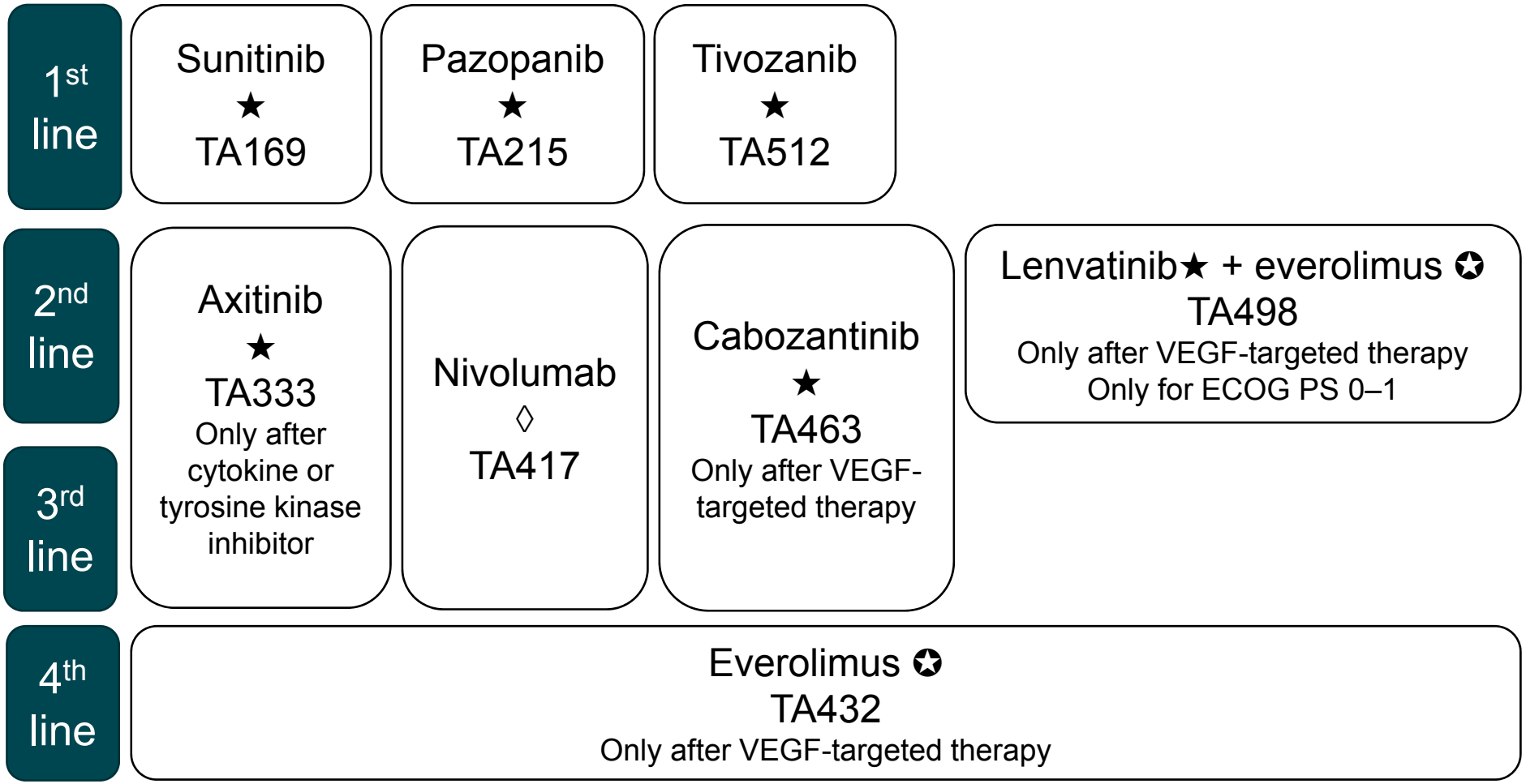
Source: Table 2 (page 9) company submission

Decision problem

	Final scope issued by NICE	Company's decision problem
Population	People with untreated, intermediate or poor risk (as per IMDC), locally advanced or metastatic renal cell carcinoma	As per the scope
Comparators*	• Pazopanib • Sunitinib	As per the scope
Outcome	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life (HRQoL)	As per the scope

**Tivozanib appraisal (Comm B) was ongoing during scoping phase*

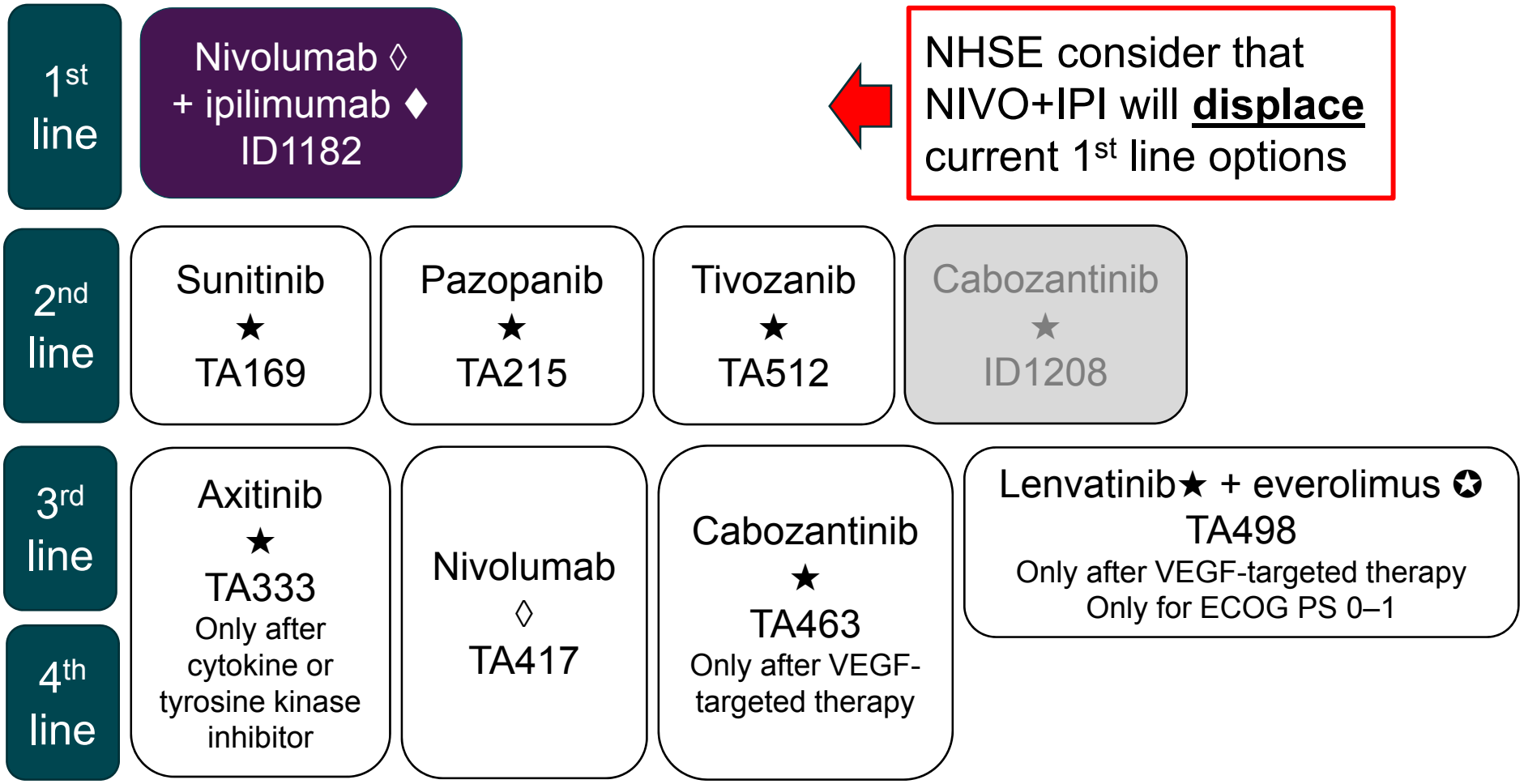
Current treatment pathway



Key; ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor
★: oral tyrosine kinase inhibitors (TKI); ✪: oral mammalian target of rapamycin (mTOR) inhibitor;
◊ **:** anti-programmed death 1 (PD-1) inhibitor; ♦: anti-CTLA-4 inhibitor

New treatment pathway

Intermediate-/poor-risk only



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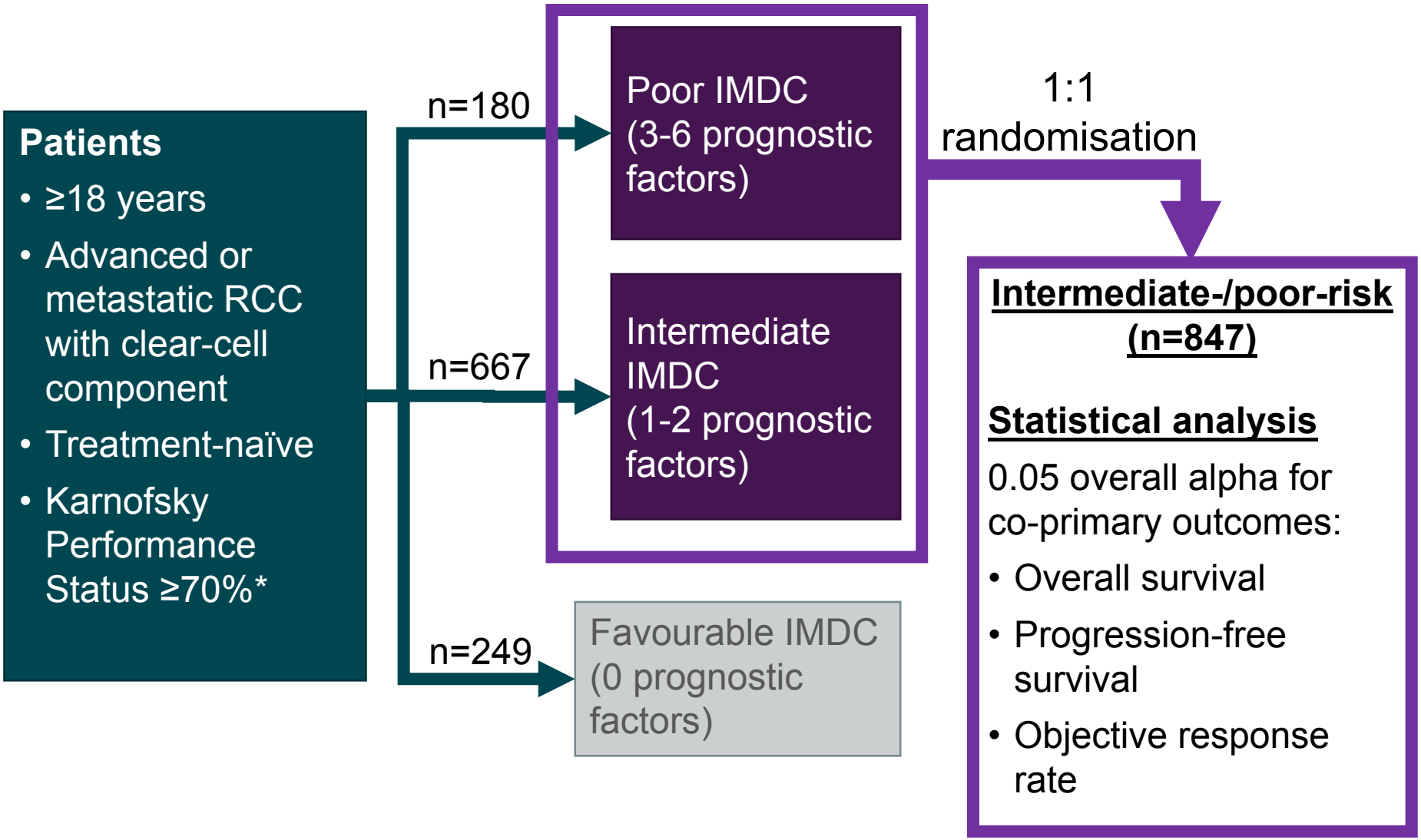
Patient perspectives

- Current treatment pathway for metastatic renal cell carcinoma is surgery, followed by either oral sunitinib or pazopanib at 1st line
- Symptoms include extreme fatigue, intestinal problems, nausea and vomiting, significant back pain, severe hand and foot syndrome, fever, night sweats, hyperthyroidism, pneumonitis, anaemia and high blood pressure. Often symptoms require additional medicines to help manage
- People want therapy which extends life, but which is more manageable than current treatment options
- People would require more hospital visits for NIVO+IPI, an intravenous therapy, than for current oral treatments, but balanced against extra travel and time is the improved side effect profile and enhanced quality of life
  - Half a day in hospital is preferable to the debilitating side effects of the oral VEGF-targeted therapies
- No groups of patients identified at 1st line who might benefit more or less from the technology than others

Key clinical evidence

- CheckMate 214 randomised controlled trial (RCT) compares NIVO+IPI with sunitinib
  - All results from August 2017 data cut; median follow-up, 25.2 months
- Company conducted a network meta-analysis (NMA) to compare NIVO+IPI with pazopanib
  - The NMA included 37 trials, but was unable to estimate overall survival hazard ratios for intermediate-/poor-risk group
  - ERG requested a simpler indirect comparison using COMPARZ trial, an RCT that compares sunitinib with pazopanib
- Company and ERG agree that CheckMate 214 and COMPARZ trial were well designed and conducted, with a low risk of bias for most domains
- ERG note that CheckMate 214 data is immature, so it is unknown whether the results at the first-interim analysis will be observed in the longer-term

CheckMate 214
Patient recruitment



CheckMate 214
Outcomes

Outcome	Definition
Co-primary outcomes	
Progression-free survival (PFS)	**Intermediate-/poor-risk patients** • *1° definition*: Time from randomisation until documented disease progression by Independent Radiology Review Committee as per RECIST 1.1 criteria, or death. Censoring for subsequent treatment 2° definition: as above – no censoring for subsequent treatment
Overall Survival	**Intermediate-/poor-risk patients** *Time from randomisation to death from any cause*
Response rates	**Intermediate-/poor-risk patients** *Proportion who achieved complete or partial response, based on IRRC assessment (as per RECIST v1.1)*
Other outcomes **(all treated patients)**	
PFS	Investigator-assessed PFS for 1° and 2° definition
Safety and tolerability	*Incidence of adverse events*, deaths and laboratory abnormalities
HRQoL	FACT-G, FKSI-19 and *EQ-5D-3L* questionnaires

Clinical outcomes used in model (company's base case) are underlined and italicised
Source: table B.5 (pages 25), company submission

CheckMate 214

Patient Characteristics

Characteristic	Intermediate / poor (n = 847)	
	NIVO+IPI (n = 425)	Sunitinib (n = 422)
Median age, years (min–max)	62 (26-85)	61 (21-85)
Male, n (%)	314 (74)	301 (71)
% Race Caucasian / Black / Asian / Other	86.8 / 1.6 / 8.9 / 2.6	87.2 / 1.4 / 9.2 / 2.1
% Karnofsky Performance Status 100 / 90 / 80 / 70	39.1 / 30.4 / 17.9 / 12.5	36.0 / 31.8 / 20.1 / 11.8
% IMDC prognostic score Favorable / Intermediate / poor	0 / 79 / 21	0 / 79 / 21
% PD-L1 expression <1% / ≥1%	74 / 26	71 / 29
% with metastasis of Lung / lymph / liver / bone	69 / 45 / 21 / 20	70 / 51 / 21 / 21

Source: adapted from table B.6 (page 22-23), company submission

ERG critique
Patient Characteristics

- Baseline characteristics were well balanced between arms
- Intermediate-/poor-risk group were very similar to the all risk group enrolled into the trial, with the obvious exception of risk status
- With a few exceptions baseline characteristics appears to be generalisable to patients who would be treated in NHS clinical practice

Characteristic	Intermediate-/poor-risk	
	CheckMate 214	**NHS clinical practice**
Median age (range)	62 (21-85)	Older
% IMDC prognostic score Intermediate / poor	61 / 16	~ 50 / 30
Prior nephrectomy	90%	~70%
Clear cell disease	100%	~75%

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CheckMate 214

Key results - intermediate-/poor-risk

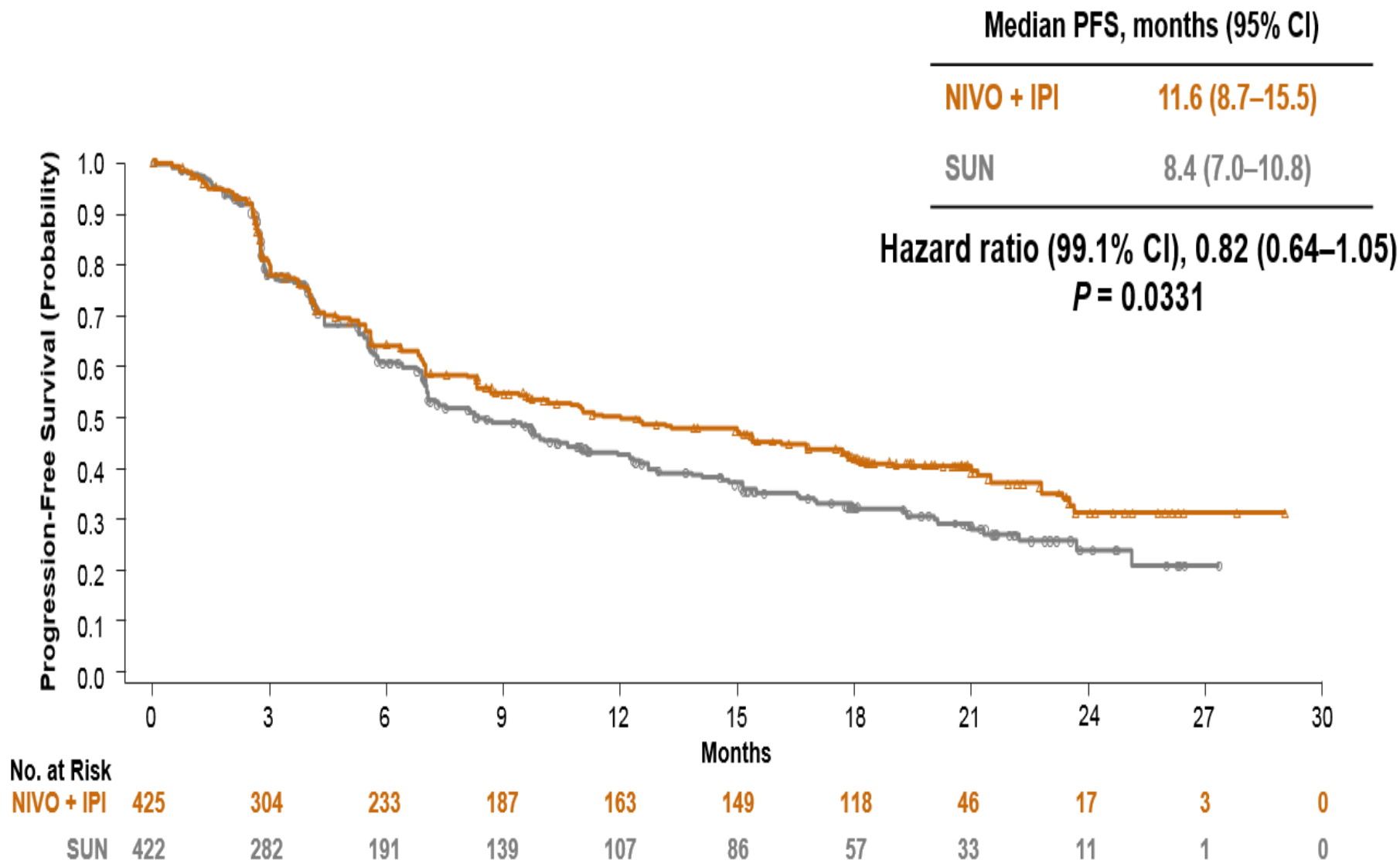
	NIVO+IPI (n = 425)	Sunitinib (n = 422)	Hazard ratio
Co-primary outcomes			
Median IRRC PFS, months (95% CI) 1° definition	11.6 (8.7-15.5)	8.4 (7.0-10.8)	0.82 99.1% CI: 0.64-1.05
Median IRRC PFS, months (95% CI) 2° definition	11.0 (8.3-15.2)	8.3 (7.0-9.8)	0.76 99.1% CI: 0.60-0.95
Median OS, months (95% CI)	NR (28.2-NE)	26.0 (22.1 – NE)	0.63 99.8% CI: 0.44-0.89
ORR, %	41.6	26.5	-
ORR difference (95% CI)	[redacted]		-
Other outcomes			
Median TTR, months	2.8	3.0	-
Median DOR, months	NR	18.2	-

IRRC, Independent Radiology Review Committee; CI, Confidence interval; PFS, Progression-free survival; OS, overall survival; ORR, overall response rate; TTR, time-to-response; DOR, Duration of response; NR, Not reached; NE, Not evaluable

Source: adapted from B.2.6 (page 29-33), company submission

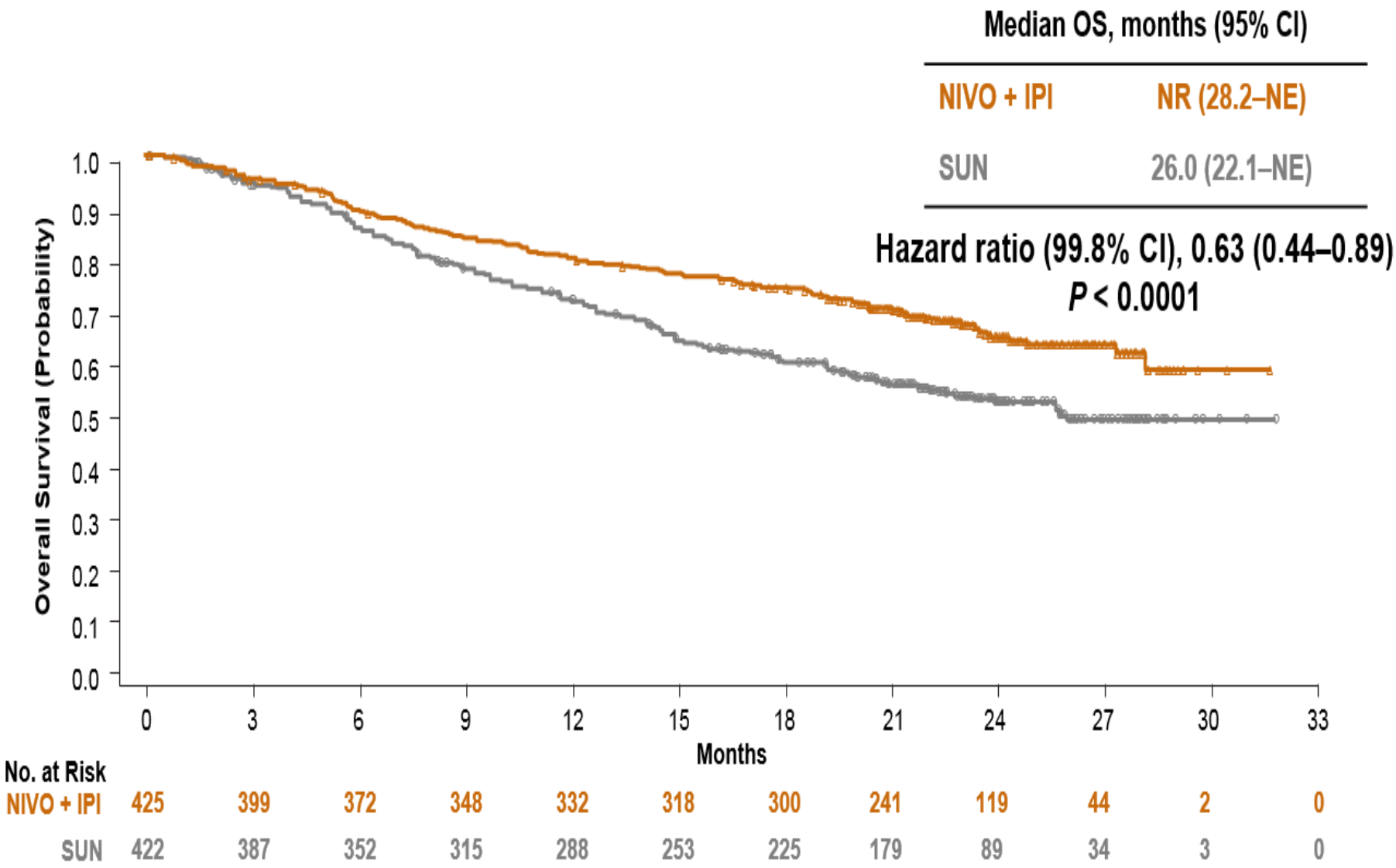
CheckMate 214

PFS 1° definition - *intermediate-/poor-risk*



CheckMate 214

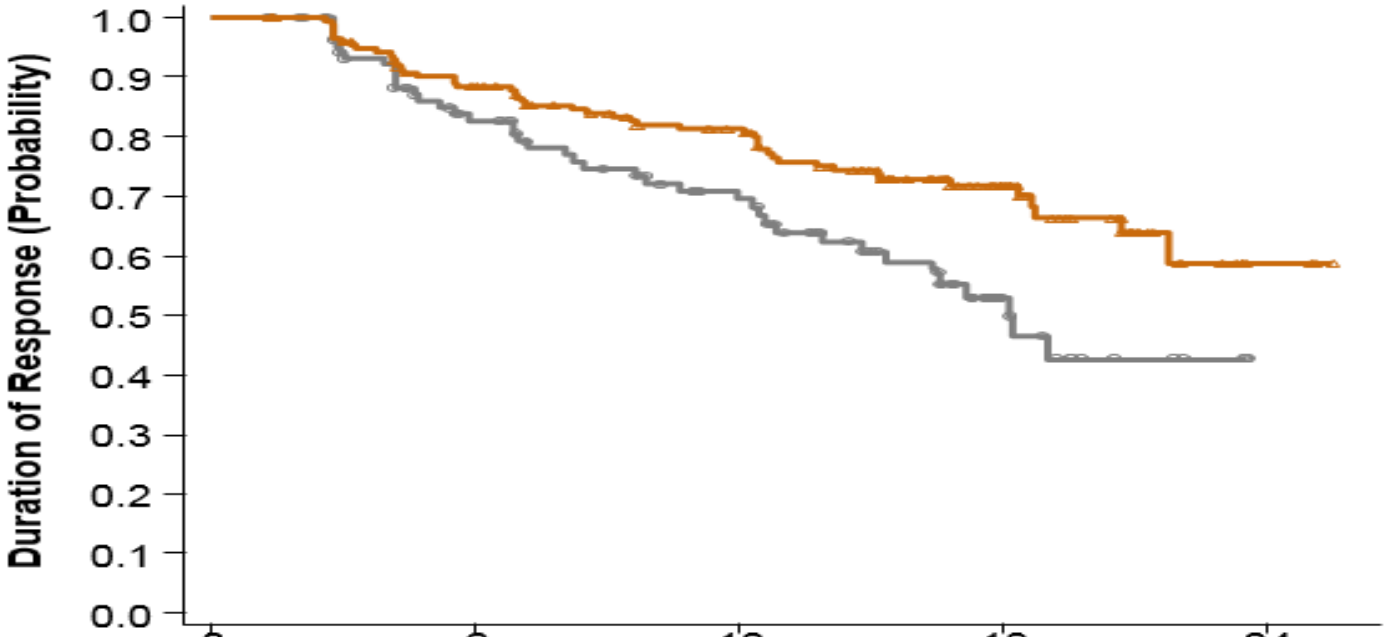
Overall survival - intermediate-/poor-risk



CheckMate 214

Duration of response – intermediate-/poor-risk

	Median duration of response, months (95% CI)	Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63



No. at Risk					
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

- Company define 30.1% of NIVO+IPI arm as ‘durable responders’, which they use to inform an immunological effect in the model

ERG Critique
Proportional hazards assumption

- Cox proportional hazards (PH) method was used to estimate the OS and PFS HRs for the CheckMate 214 trial
- Hazard ratios are not an appropriate summary of treatment effect when the PH assumption does not hold
- The ERG considers that the PH assumption may be violated for:
  - Intermediate-/poor-risk OS and PFS (1° and 2° definitions)
  - Intermediate-risk OS and PFS (1° and 2° definitions)
  - Poor-risk PFS (1° and 2° definitions)
- It appears that the PH assumption holds for poor-risk OS data
- Consequently, the ERG considers that the reported HRs for OS and PFS data from the CheckMate 214 trial should be interpreted with caution
- It is not possible to know whether the reported HRs would overestimate or underestimate the effect of NIVO+IPI versus sunitinib

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ERG Critique

Progression-free survival

- ERG prefer using 2° definition. They consider censoring for subsequent treatment may be an example of informative censoring*
- IRRC- and investigator-assessed PFS medians are different, but the hazard ratio is not. This indicates that the PH assumption is violated

Source: figure 22 (page 108), ERG report

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Pre-specified subgroup results – prognostic risk group

		NIVO+IPI	Sunitinib	Hazard ratio
Intermediate-risk (n=667)				
Median IIRC PFS, months (95% CI)	1° definition	[redacted]	[redacted]	[redacted]
	2° definition	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)		[redacted]	[redacted]	[redacted]
ORR, %		[redacted]	[redacted]	[redacted]
ORR difference (95% CI)		[redacted]		[redacted]
Poor-risk (n=180)				
Median IIRC PFS, months (95% CI)	1° definition	[redacted]	[redacted]	[redacted]
	2° definition	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)		[redacted]	[redacted]	[redacted]
ORR, %		[redacted]	[redacted]	[redacted]
ORR difference (95% CI)		[redacted]		[redacted]

CI, Confidence interval; PFS, Progression-free survival; OS, overall survival; ORR, overall response rate; NR, Not reached; NE, Not evaluable

Source: Adapted from table 8 and 9 (page 51-52), ERG report

ERG Critique

Prognostic risk groups (I)

- Although HRs indicate no evidence of a difference, visual inspection suggest response to treatment may be different in the two risk groups
- As majority of events in the datacut are in smaller, poor-risk group, long-term trends will likely reflect trends in the intermediate-risk group

Intermediate-risk OS

Poor-risk OS

Source: adapted from figure 11 and 12 (page 99-100), ERG report

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ERG Critique

Prognostic risk groups (II)

- The ERG agree that all results for separate prognostic groups should be interpreted with caution, as the analyses were post-hoc analyses
- ERG considers intermediate-/poor-risk group combined most appropriate to consider for decision making, particularly given NIVO+IPI is to be licensed for this population and the immaturity of OS data available

intermediate-risk inv-assess PFS (2°) poor-risk inv-assess PFS (2°)

Source: adapted from figure 15 and 16 (page 102), ERG report

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Pre-specified subgroup results – PD-L1 status

	NIVO+IPI	Sunitinib	Hazard ratio
PD-L1 tumour expression ≥1%; intermediate-/poor-risk (n=214)			
Median IRRC PFS, months (95% CI) 1° definition	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]
ORR, %	[redacted]	[redacted]	[redacted]
ORR odds ratio (95% CI)	[redacted]		[redacted]
PD-L1 tumour expression <1%; intermediate-/poor-risk (n=562)			
Median IRRC PFS, months (95% CI) 1° definition	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]
ORR, %	[redacted]	[redacted]	[redacted]
ORR odds ratio (95% CI)	[redacted]		[redacted]

CI, Confidence interval; PFS, Progression-free survival; OS, overall survival; ORR, overall response rate; NR, Not reached; NE, Not evaluable
Source: Adapted from E.4 (page 70), company submission

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CheckMate 214

Subsequent therapies – all treated patients

- Company note that subsequent therapies used in CheckMate 214 do not reflect current UK practice, and use clinical opinion to inform the model
  - ERG caution it is unknown how this would impact overall survival

	NIVO+IPI (n=550) n (%)	Sunitinib (n = 546) n (%)
Any subsequent therapy	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]
Subsequent systemic therapy	[redacted]	[redacted]
Common subsequent systemic therapy:		
Other Chemotherapy	[redacted]	[redacted]
Anti-PD-1 (nivolumab, pembrolizumab)	[redacted]	[redacted]
Experimental drugs	[redacted]	[redacted]
Other immunotherapy (IFN, IFN-α, IL-2, investigational immunotherapy)	[redacted]	[redacted]

Source: Table B.13 (page 51), company submission

NIVO+IPI vs pazopanib indirect comparison
Company submission

- To estimate OS and PFS for the intermediate-/poor-risk group the company investigated an indirect comparison using network of **37 trials**
- Company consider results unreliable:
  - Few studies reported results for the intermediate-/poor-risk group
  - MSKCC (rather than IMDC) scoring system used in all comparator studies
  - Results lack face validity*
- Company use CheckMate 214 data in model. Except for treatment duration, company assume pazopanib is clinically equivalent to sunitinib

Comparison	Fixed-effect model		Random-effect model (non convergent)	
	PFS HR (95% CrI)	**OS HR (95% CrI)**	**PFS HR (95% CrI)**	**OS HR (95% CrI)**
NIVO+IPI vs. sunitinib	0.82 [0.68, 0.99]	0.63 [0.5, 0.8]	0.82 [0.01, 58.6]	0.63 [0.01, 30.85]
NIVO+IPI vs. pazopanib	0.78 [0.61, 1.00]	Data not available	0.78 [0.00, 306.74]	Data not available

Source: Adapted from table B.10 (page 46), company submission;

NIVO+IPI vs pazopanib indirect comparison

Response to clarification

- ERG noted that it is possible to conduct a simpler indirect comparison using CheckMate 214 and the COMPARZ (sunitinib vs. pazopanib) trials
- The company submitted an updated analysis at clarification. It notes that substantial uncertainty remains as:
  - COMPARZ uses the MSKCC scoring system
  - COMPARZ separately reports poor- and intermediate-risk groups, and only intermediate-risk results available for PFS
  - COMPARZ does not provide patient characteristics by risk group
  - COMPARZ trial not powered for intermediate-/poor-risk (69% of full trial population)

Comparison	Indirect treatment comparison (Bucher's method)	
	PFS HR (95% CI)*	**OS HR (95% CI)**
NIVO+IPI vs. sunitinib	[redacted]	[redacted]
NIVO+IPI vs. pazopanib	[redacted]	[redacted]

Source: Adapted from response to clarification query A17 (page 25-31), company response to clarification

NIVO+IPI vs pazopanib indirect comparison
ERG critique

- ERG agree with limitations highlighted with requested indirect comparison, but consider it most robust estimate of relative effectiveness
  - ERG disappointed company did not request data directly from COMPARZ authors
- Based on the baseline characteristics for the overall population, patients in both trials appeared to be broadly similar
  - baseline characteristics across risk groups broadly similar in CheckMate 214. No reason to believe COMPARZ trial different
- However the ERG also prefer to maintain assumption sunitinib and pazopanib are clinically equivalent in the model. This is because:
  - agree with the limitations highlighted by company
  - exact definitions of PFS may have differed between trials
  - clinical advice is that sunitinib and pazopanib are widely considered to be clinically equivalent
  - previous appraisals have accepted clinical equivalence

CheckMate 214

Adverse events – Overview

CheckMate 214

drug-related Grade ≥3 *AEs included in model - intermediate-/poor-risk*

Health-related quality of life (HRQoL)

EQ-5D and FACT-G – all randomised patients

EQ-5D-3L

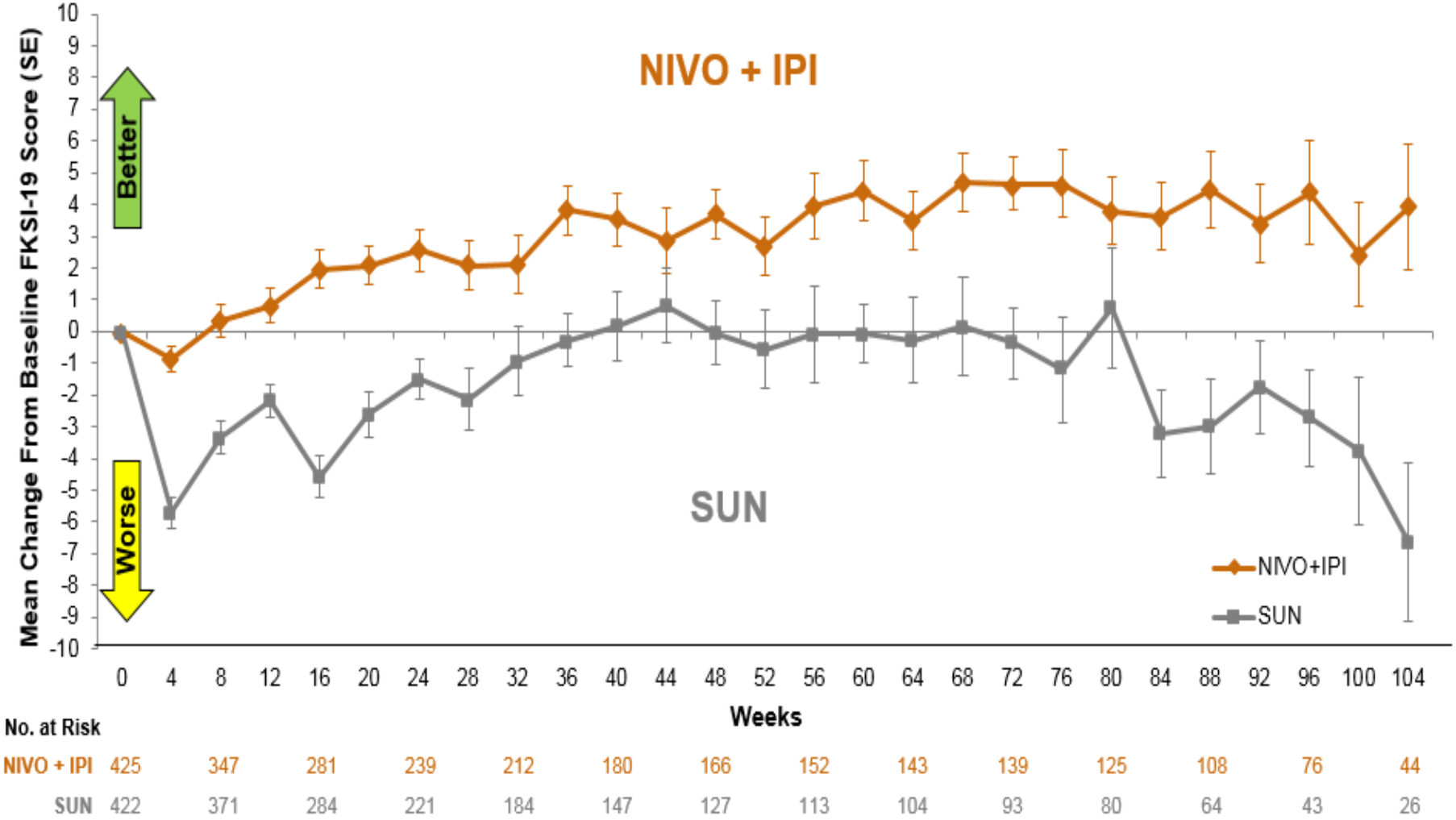
- [redacted]
- Visual analogue score (VAS) general health assessments exceeded baseline values in [redacted] of people treated with NIVO+IPI and [redacted] of people treated with sunitinib.

FACT-G

- FACT-G questionnaire completed by [redacted] of people treated with NIVO+IPI and [redacted] of people treated with sunitinib
- Over first year of follow-up, quality of life assessments exceeded baseline values for [redacted] of people treated with NIVO+IPI and [redacted] of people treated with sunitinib

Health-related quality of life (HRQoL)

FKSI-19 - intermediate-/poor-risk



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ERG critique

Health-related quality of life

- The results show that HRQoL was [redacted] over time for patients treated with NIVO+IPI compared with patients treated with sunitinib
- However only patients who remained on treatment were asked to complete the questionnaires (although they were asked to completed questionnaires on two occasions after their last dose)
- Therefore, although the response rate is high, the proportion of patients eligible to complete the questionnaire drops substantially
- For FKSI-19 the proportion of patients on treatment was 54% after 24 weeks, 35% after 48 weeks and 8% after 104 weeks
- Therefore the HRQoL results must be treated with a degree of caution, particularly results from 24 weeks and beyond

Key issues – clinical effectiveness

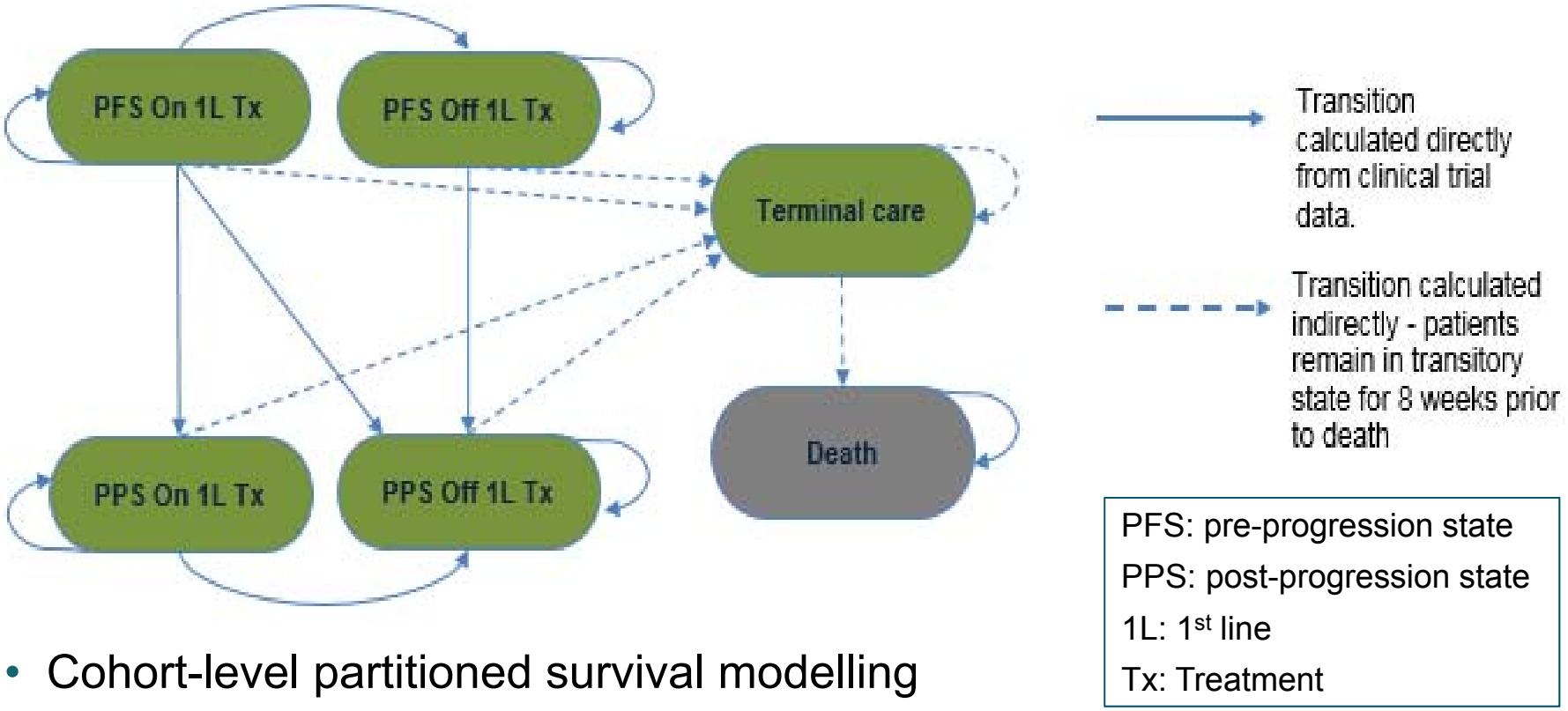
- Where will the technology be used in the treatment pathway?
- Are there patients who can tolerate nivolumab, but not ipilimumab?
- Is the clinical evidence generalisable to UK clinical practice?
- Which definition and assessment of PFS is more appropriate for decision-making:
  - with or without censoring for subsequent treatments?
  - investigator or IRRC assessed?
- Is there value in an indirect treatment comparison?
  - If so, which approach to the indirect treatment comparison is more appropriate to inform decision-making?
- Is the technology clinically effective?
  - Are there any groups who appear to benefit more or less from the technology than others?
  - Are the results likely to be maintained in the long-term?

Cost effectiveness evidence

Company submission section 5

Patient Access Schemes (PAS) are available for subsequent treatment options. Cost-effectiveness estimates which include these are available in a confidential appendix to this document

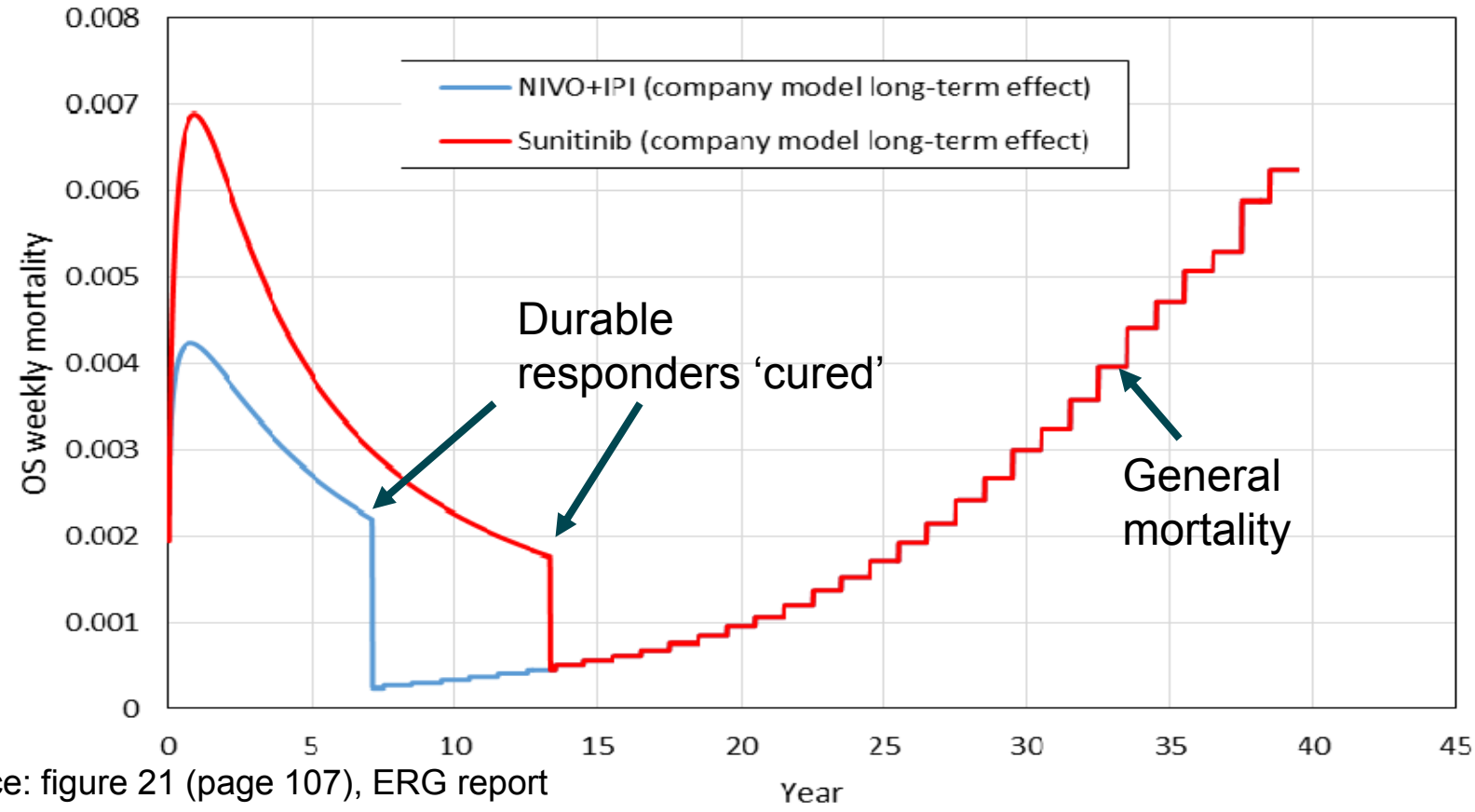
Model structure



- Cohort-level partitioned survival modelling
- UK NHS perspective
- Starting age – 60.5; Time horizon – 40 years; Cycle length – 1 week
- 3.5% discounting for costs and health benefits

Immunological effect
Company approach

- Company assume durable responders (30.1% responding at latest CheckMate 214 datacut) at either 1st or 2nd line return to an OS equal to general mortality.
  - i.e. Once 30% people remain alive, mortality rate 'jumps' to general mortality



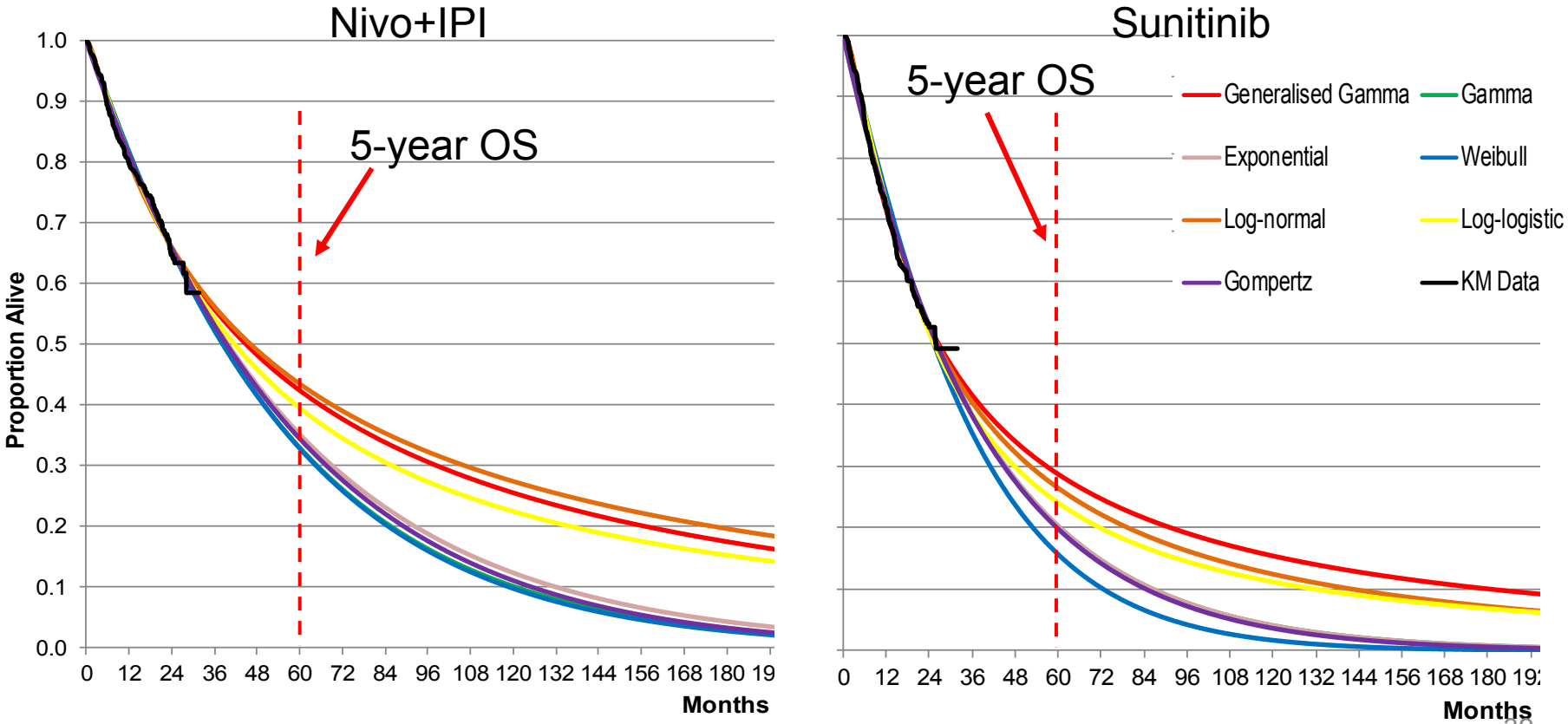
Source: figure 21 (page 107), ERG report

Immunological effect
Previous committee considerations

- Committees have not previously accepted immunotherapies would ‘cure’ a proportion of patients
- Committees have considered the ‘long tail’ seen in melanoma may not be applicable to other indications
- Similar approach used in TA417 (nivolumab monotherapy 2nd line RCC)
  - Committee noted there was little evidence to support an immunological effect, and preferred that it was removed, but it was willing to consider scenarios with predictions of better survival in its decision-making
- An immunological effect has been accepted in combination with a stopping rule. i.e. some patients would receive some continued treatment benefit **if** treatment was stopped before progression
  - Committees have concluded the magnitude of any immunological effect to be highly uncertain

Overall survival
Company approach

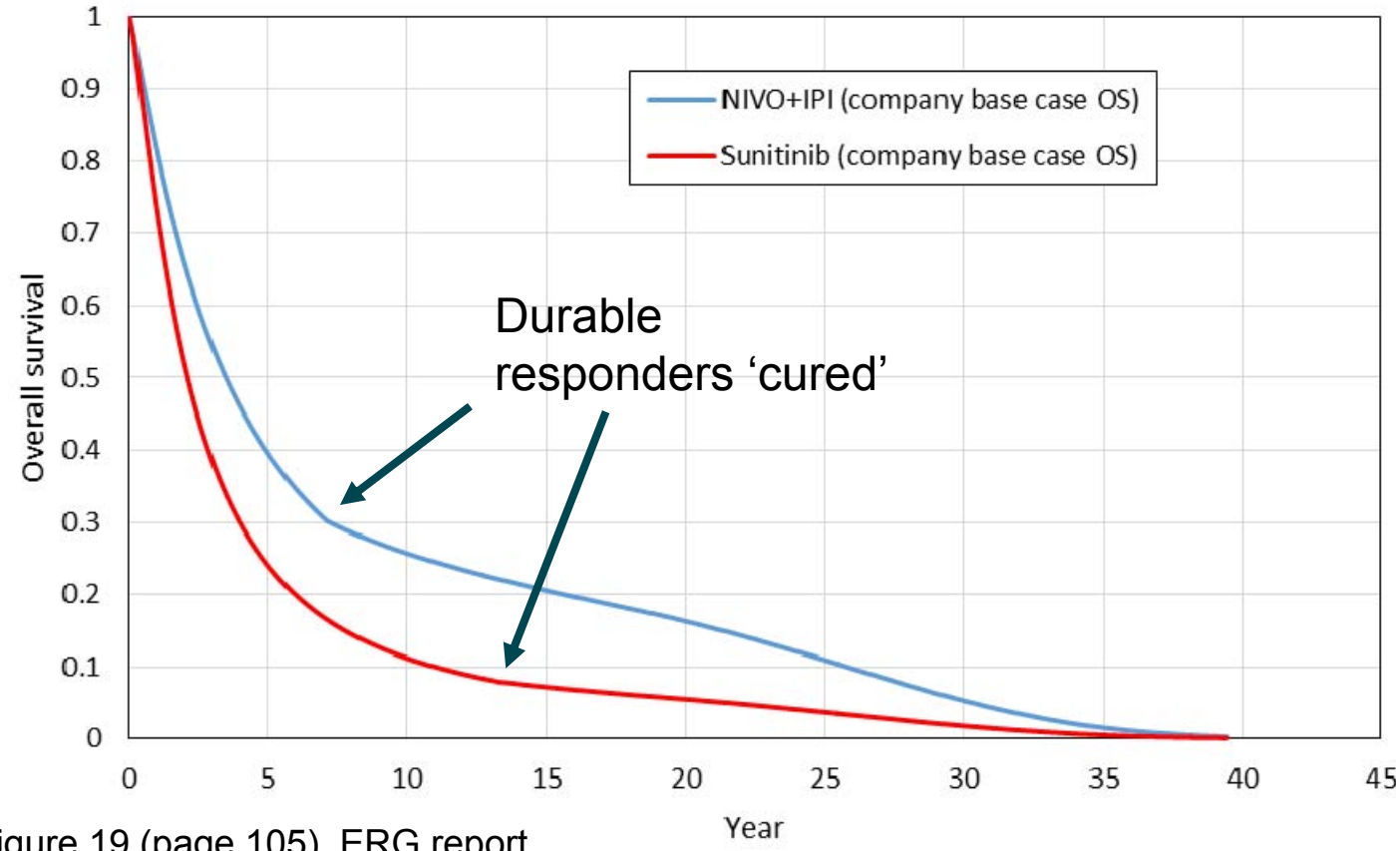
- Company use fully-fitted parametric curves to extrapolate overall survival
- Log-normal curve best statistical fit, but more conservative log-logistic curve chosen as it has clinically plausible 5-year overall survival between 35% - 45%



Source: figure B.17 and 18 (page 77), company submission

Overall survival
Company approach (III)

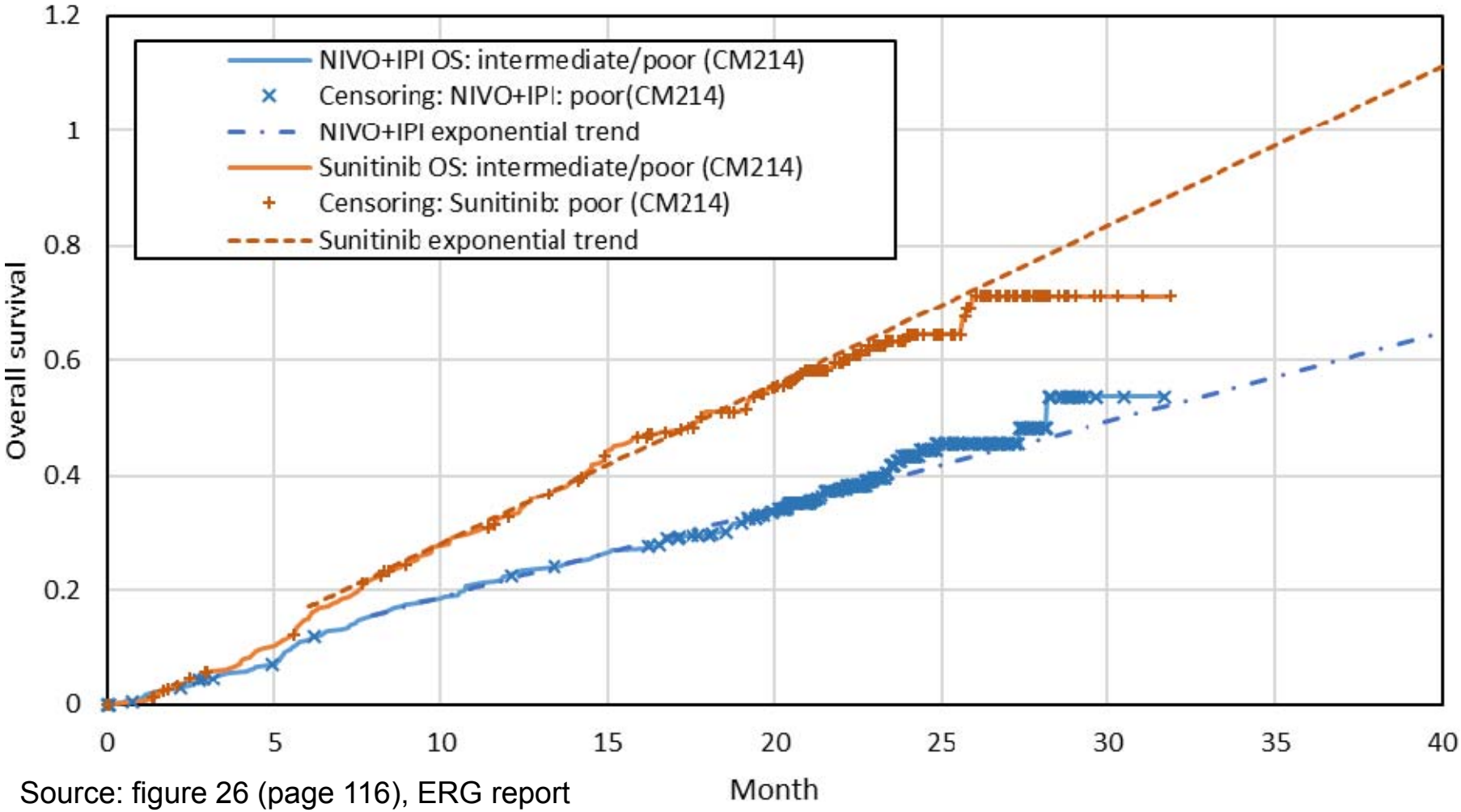
- Company base case combines the ‘continued immunological effect ’ and normal ‘fully fitted’ component curves
- Continued immunological effect curve given a 0.5 weighting to represent a 50% likelihood of an immunotherapeutic effect



Source: figure 19 (page 105), ERG report

Overall survival
ERG critique (I)

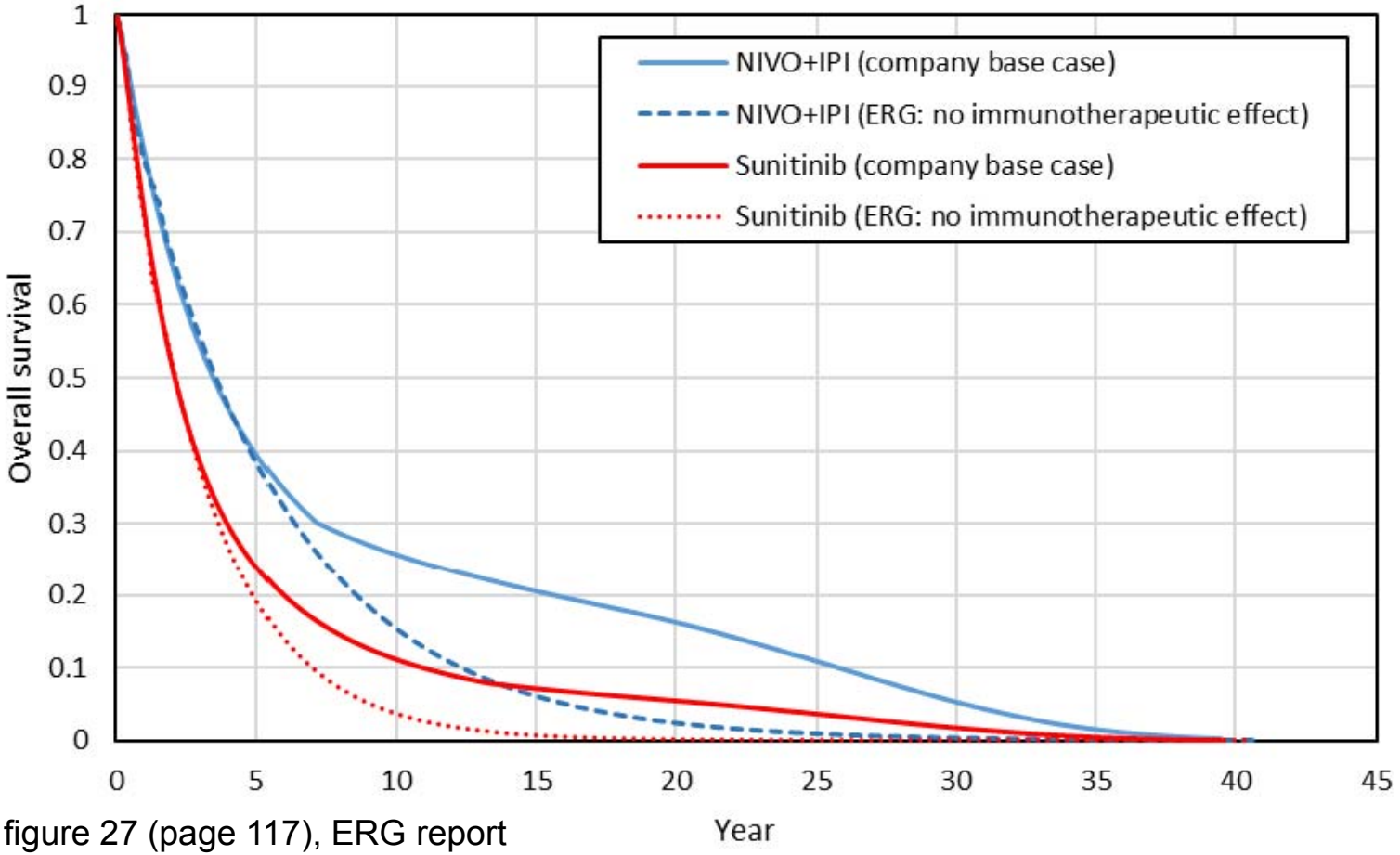
- The ERG consider cumulative hazard plots show an exponential trend (i.e the hazard rate is constant) from around 7 months.



Source: figure 26 (page 116), ERG report

Overall survival
ERG critique (II)

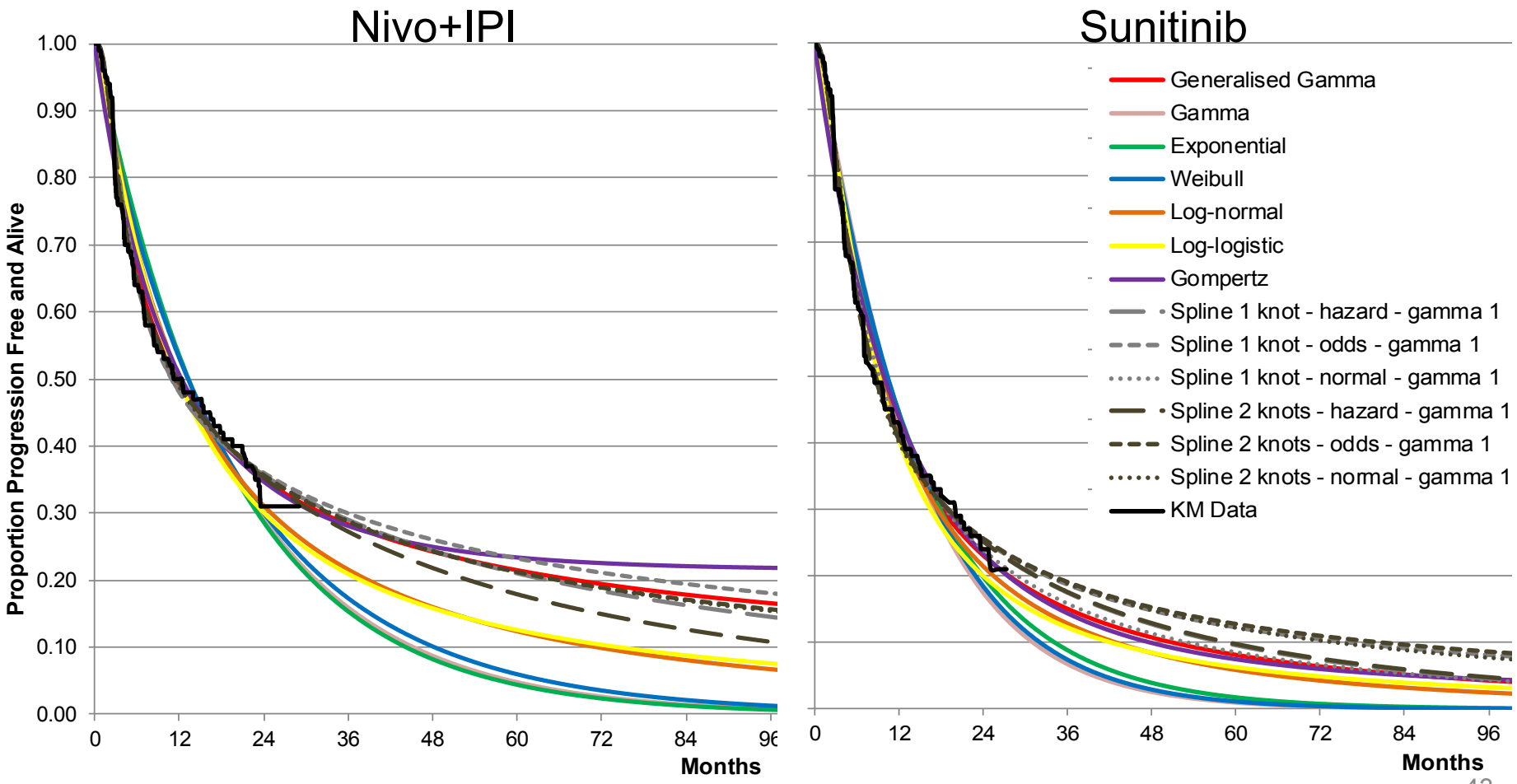
- ERG append exponential curves to the K-M data at 22 months for each arm.
- ERG do not consider there is good evidence for responders to be ‘cured’. They note a proportion may still achieve long-term survival with exponential tail



Source: figure 27 (page 117), ERG report

Progression-free survival
Company approach (I)

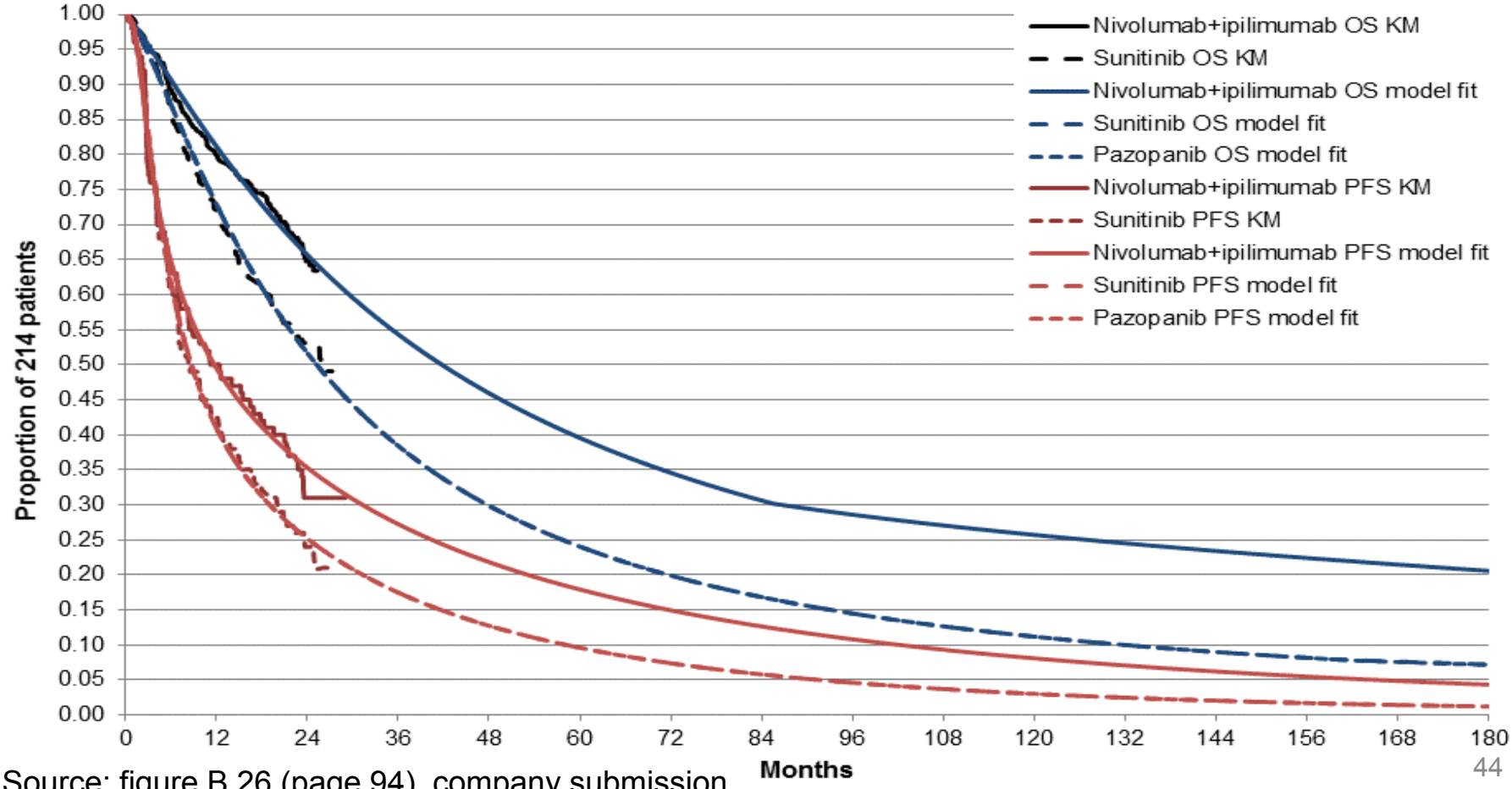
- Standard parametric models did not provide a particularly good fit to the data, either visually or statistically



Source: figure adapted from B.24 and B.25 (page 92), company submission

Progression-free survival
Company approach (II)

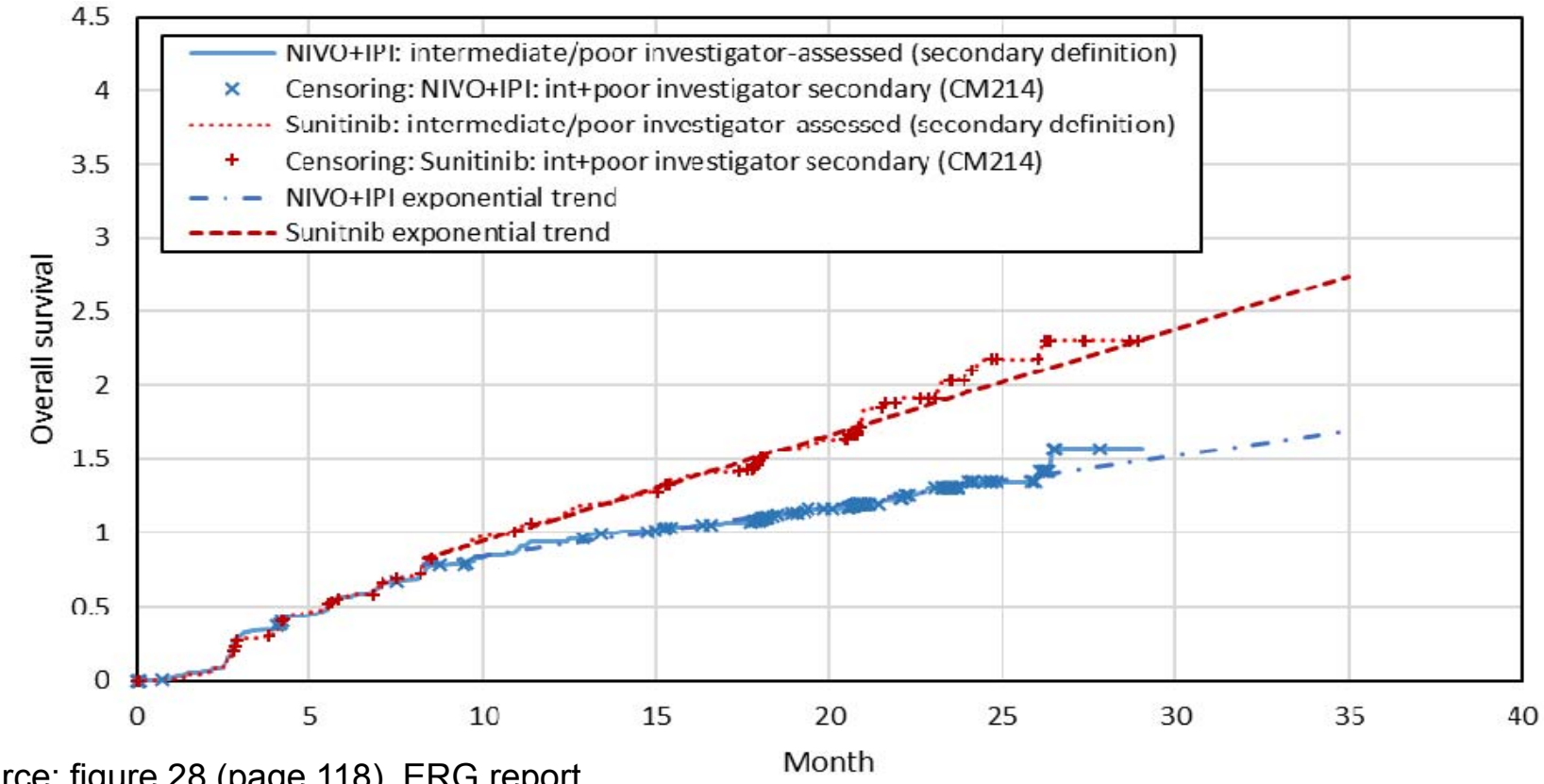
- Company fit spline 2-knot hazard to NIVO+IPI and a spline 1-knot hazard model fit to sunitinib arm
- A limit is built into the model whereby PFS cannot exceed OS



Source: figure B.26 (page 94), company submission

Progression-free survival
ERG critique (I)

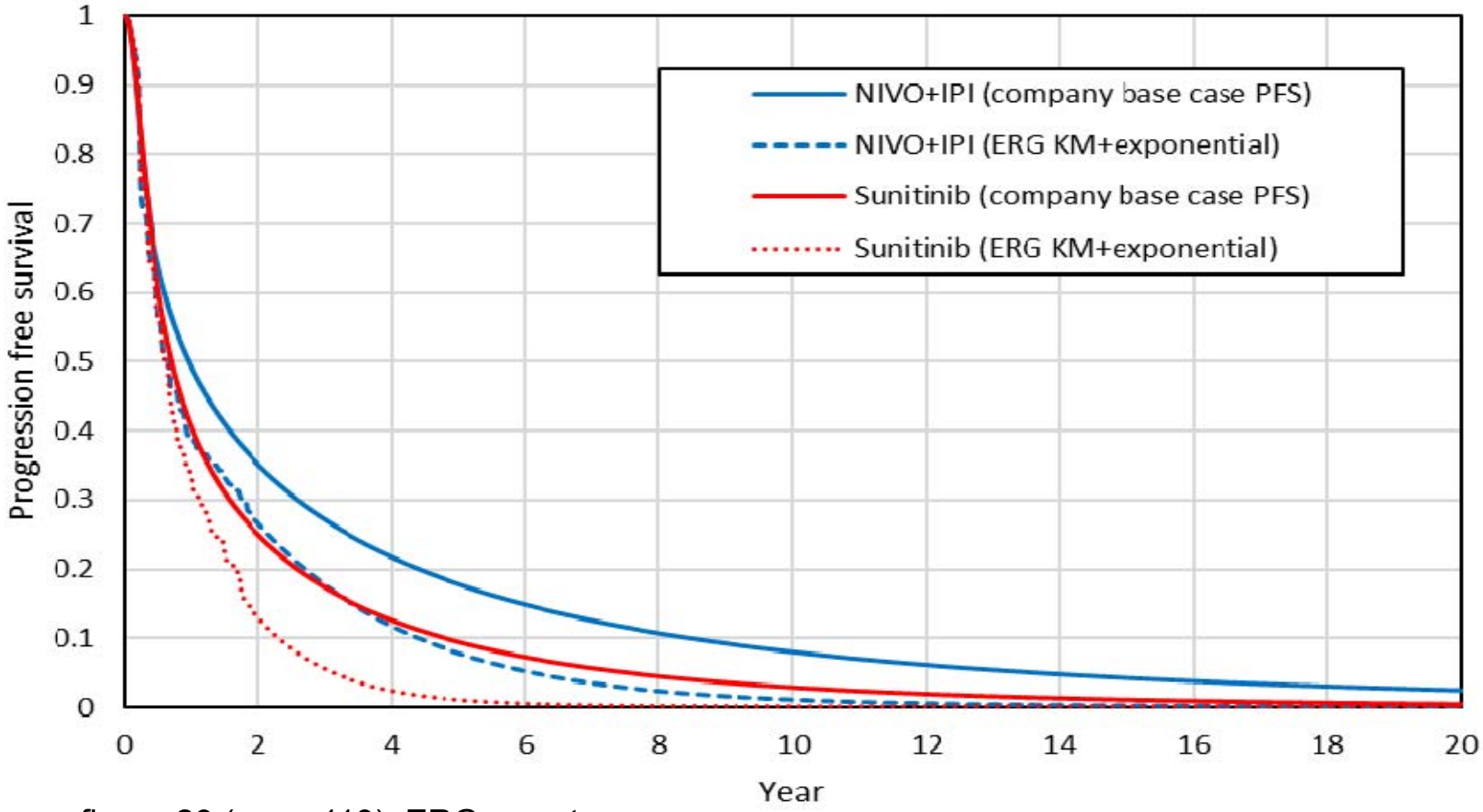
- ERG preferred to use investigator-assessed, 2° definition of PFS as:
  - Costs will be predicated upon tumour assessments conducted by clinician
  - 1° definition censors subsequent treatment, which may differ between arms
- ERG consider exponential trend begins around 8 months



Source: figure 28 (page 118), ERG report

Progression-free survival
ERG critique (II)

- ERG prefer to use KM data as far as possible (NIVO+IPI: 22 months; sunitinib: 21 months)
- Exponential curve fitted, calculated using data from 8 months onwards



Source: figure 29 (page 119), ERG report

Time to treatment discontinuation (TTD)

Company approach

- Company use [redacted] parametric curves to extrapolate TTD. This is to ensure [redacted] to meet with clinical expectation
- For pazopanib company apply a hazard ratio of 0.95 to sunitinib curve
- Company assume NIVO+IPI will have stopping rule at 5 years

Source: figure B.22 (page 102), company submission

Stopping rule
Previous committee considerations

- Stopping rules included in recommendations for 8 out of 18 published and ongoing technology appraisals for PD-1/PD-L1 inhibitors*
- Of the remainder:
  - 3 appraisals: Accepted stopping rule, but technology not recommended
  - 3 appraisals: Concluded stopping rules inappropriate or could not be considered
  - 1 appraisal: Considered cost effectiveness both with and without a stopping rule
  - 3 appraisals: not discussed
- Committee considerations have concentrated on:
  - Marketing authorisations for the technologies
  - Inclusion of maximum durations in clinical trial protocols
  - Impact on treatment costs
  - Impact on clinical effectiveness and a continued treatment benefit
  - Implementation of the stopping rule

**Includes appraisals for nivolumab, pembrolizumab, atezolizumab and avelumab for which published ACDs or FADs are available*

Time to treatment discontinuation (TTD)

ERG critique (I)

- ERG consider company's [redacted] curve a poor visual fit to CheckMate 214 data
- ERG note that the company curve with the best statistical and visual fit (below) would have [redacted] if the stopping rule was removed

Source: figure 24 (page 111), ERG report

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Time to treatment discontinuation (TTD)

ERG critique (II)

- Cumulative hazard plot suggest an [redacted] (NIVO+IPI) and [redacted](sunitinib)
- The marketing authorisation for NIVO+IPI does not specify a stopping rule
- ERG do not consider applying hazard ratio to sunitinib TTD to estimate pazopanib is justified, and prefer that they are considered equivalent because:

- Inappropriate to apply a hazard ratio to a [redacted] curve
- data used to estimate the hazard ratio does not include confidence intervals
- PFS is considered equivalent

Source: figure 30 (page 120), ERG report

Time to treatment discontinuation (TTD)
ERG critique (III)

- The ERG prefers to append exponential curves to the K-M data for both treatments at 22 months, remove the 5-year stopping rule, and assume TTD is equivalent for sunitinib and pazopanib

Source: figure 32 (page 121), ERG report

Utility values
Company approach

- Company carried out a regression-based analysis to derive mean utility values using responses to the EQ-5D-3L questionnaire from the CheckMate 214 trial
- Company investigate the impact of three main effects:
  - treatment arm
  - treatment status
  - progression status
- Company use a regression-based model which includes treatment arm and treatment status, plus an interaction term (model 5)

Utility values
ERG critique

- Based on AIC statistics the ERG prefers the model which also includes progression status (model 7)

State	Company preferred Model 5: treatment status and treatment arm		ERG preferred Model 7: treatment status, treatment arm and progression status	
	NIVO+IPI	Sunitinib	NIVO+IPI	Sunitinib
PFS (on treatment)	0.793	0.751	0.793	0.750
PFS (off treatment)	0.719	0.699	0.737	0.703
PPS (on treatment)	0.793	0.751	0.794	0.763
PPS (off treatment)	0.719	0.699	0.701	0.694

Source: table 33 (page 122), ERG report

Resources use and costs

- Dose intensity sourced from CheckMate 214 (NIVO+IPI and sunitinib) and from TA217 (sunitinib and pazopanib)
- Resource use assumptions informed from nivolumab for previously treated advanced renal cell carcinoma (TA417; 2016) and validated using clinical review
  - Costs updated using Personal Social Services Research Unit (PSSRU) or NHS Reference Costs to reflect 2016–2017 prices
- Cost of grade 3/4 treatment-related adverse events which occur in ≥15% of treated patients (any grade) included
  - Costs sourced by searching previous NICE appraisals in RCC

- ERG includes the impact of including administration costs for treatment with sunitinib and treatment with pazopanib. Applying a unit cost of £164 per cycle (SB11Z Deliver exclusively oral chemotherapy [outpatient])

Subsequent treatment use

- The company considers the subsequent treatments used in CheckMate 214 do not represent current UK clinical practice. Clinical opinion informs cost of subsequent treatment use (no adjustment to clinical outcomes)
- ERG prefer estimates to be linked directly to the source of OS, PFS and TTD outcomes, as outcomes linked to treatments patients actually received

	Company assumption (clinical opinion*)		ERG assumption (CheckMate 214)		TA512 clinical opinion
	From				
To	NIVO+IPI	Sunitinib	NIVO+IPI	Sunitinib	Sunitinib
Nivolumab	-	60%	[redacted]	[redacted]	30%
Sunitinib	-	-	[redacted]	[redacted]	-
Pazopanib	-	-	[redacted]	[redacted]	-
Axitinib	30%	-	[redacted]	[redacted]	50%
Cabozantinib	30%	20%	[redacted]	[redacted]	-
Everolimus	-	-	[redacted]	[redacted]	10%

*Company clinical opinion assumes NIVO+IPI would **replace** 1st line. NHSE indicates it would **displace** 1st line, which would lead to sunitinib, pazopanib and tivozanib being available as subsequent therapies
Source: adapted from table B.38 and B.39 (page 124-125), company submission

ERG Comments
Conclusions

- The company provided a detailed submission that met the requirements of NICE's scope for the base case analysis. The ERG's requests for additional information were addressed to a good standard
- Variant of the model structure has been used in the modelling of similar treatments in a previous NICE STA
- There remains considerable uncertainty in the modelling of overall survival. Data from the CheckMate 214 trial are immature and many people left the study before an event had occurred
- Uncertainty remains around the existence and/or form of any immunotherapeutic effect on survival
- Differences between the company's and ERG's preferred analysis are principally a result of the ERG's modelling of OS, which decreases incremental life years and QALYs substantially but also decreases incremental costs, and the ERG's modelling of TTD, which increases incremental costs

Innovation

The company considers NIVO+IPI innovative because:

- 1st immunotherapeutic agent licensed for use in first-line metastatic RCC. Represents a ‘step-change’ in management of this disease for patients
- Awarded with Promising Innovative Medicine designation (Sept 2017)
- 1st-line current clinical practice is currently restricted to systemic agents of one class (VEGFR TKIs) that have no proven significant benefit on OS and can be associated with significant toxicity.
- NIVO+IPI offers patients an alternative treatment modality, which has demonstrated an unprecedented survival benefit in the treatment-naïve setting compared with current standard of care
- We would anticipate the health-related benefits, such as improved survival and response benefits, to be captured in the quality-adjusted life year (QALY) calculation

End-of-life criteria – life expectancy

Treatment is indicated for patients with a short life expectancy, normally less than 24 months

- Committee previously considered that this criterion is **not** meet for the general RCC population (i.e. including favourable-risk group) (TA512)
- CheckMate 214 trial is the only source of overall survival evidence for combined intermediate-/poor-risk population (see next slide for data) However CheckMate 214 includes 3.7 times as many patients with intermediate risk status than poor risk status. Which is likely higher than clinical practice (~1.7 times as many)
  - Therefore CheckMate 214 trial may be overestimating life expectancy for the intermediate/poor risk group as a whole

End-of-life criteria
Intermediate-/poor-risk group

Preferred assumptions	Life expectancy of comparator		Life extension of NIVO+IPI	
	Median OS (95% CI) (trial data)	Mean OS (modelled)	Hazard ratio (99.8% CI) (trial data)	Mean LYGs (modelled)
Company	26.0 months (22.1-NE)	54.3 months	0.63 0.44-0.89	3.51 years
ERG		36.3 months		2.22 years

Note: committee has previously considered mean estimates from the model more relevant for life expectancy considerations (TA516)

End-of-life criteria

Intermediate-risk and poor-risk

No mean estimates of OS for the separate prognostic risk groups available

Study	Median sunitinib OS months (95% CI)	
	Intermediate risk	Poor risk
International, population-based IMDC (2013)	22.5	7.8
Population-based (Czech Republic) modified MKSCC and IMDC (2015)	MKSCC: 28.5 IMDC: 24.8	MKSCC: 10.6 IMDC: 9.3
Population-based (Netherlands) modified MKSCC (2016)	2008-10: 14.6 2011-13: 16.6	2008-10: 6.1 2011-13: 6.5
Global expanded access programme IMDC assessed (2015)	18.9	6.2
CheckMate 214 trial IMDC assessed (Not published)	[redacted] (25.2 months follow-up)	[redacted]
COMPARZ trial MKSCC assessed risk (2013)	Pazopanib 26.9 Sunitinib 26.1	Pazopanib 7.7 Sunitinib 9.9

Source: adapted from table 37 (page 129), ERG report

- Both prognostic risk groups would meet the life extension criteria:
  - Intermediate-risk group HR (95% CI): [redacted]
  - Poor risk group HR (95% CI): [redacted]

Key issues – cost effectiveness (I)

- Should an immunotherapeutic effect be included for NIVO+IPI?
  - If so, what proportion of people would be expected to benefit, and would their risk of death be equal to general mortality?
- Which definition and assessment of PFS should be used to inform the model?
- Should a stopping rule for NIVO+IPI be included?
  - If so, at what year should it be implemented and what continued treatment benefit would there be?
- Should treatment duration of pazopanib be assumed equal to sunitinib?
- What extrapolations should be used for progression-free survival, overall survival, and time-to-treatment discontinuation?

Key issues – cost effectiveness (II)

- Which regression model should be used to estimate utility values?
- Should administration costs for treatment with sunitinib and treatment with pazopanib be included?
- Should subsequent treatment use be sourced from CheckMate 214 or informed by clinical opinion?
  - What proportions would best reflect NHS clinical practice?
- Are there any innovation considerations to take into account?
- Is it reasonable to consider NIVO+IPI meets EoL criteria for:
  - the combined intermediate-/poor-risk population?
  - the intermediate-risk population?
  - the poor-risk population?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

5 February 2018

File name	Version	Contains confidential information	Date
ID1182_BMS_RCC_DocumentB_Updated Redacted	**2.0**	**Yes**	**Updated CIC submitted on 24-07-2018**

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 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission focuses on patients with previously untreated, intermediate-/poor-risk advanced or metastatic renal cell carcinoma (herein referred to as advanced RCC). The proposed population could be seen as narrower than the anticipated marketing authorisation (adult patients with intermediate-/poor-risk advanced renal cell carcinoma) because the evidence base on nivolumab in combination with ipilimumab (hereafter referred to as NIVO+IPI) is limited to the previously untreated population. Of note, this is in line with the final scope issued by NICE which was based on the anticipated marketing authorisation at the time of consultation; application was filed for the treatment of untreated, advanced RCC in adults with intermediate- or poor-risk disease.

The decision problem addressed within this submission is presented 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 untreated, intermediate or poor risk (as per International Metastatic Renal Cell Carcinoma Database Criteria), advanced or metastatic renal cell carcinoma	Adult patients with previously untreated, intermediate-/poor-risk, advanced renal cell carcinoma (advanced or metastatic)	N/A
Intervention	Nivolumab in combination with ipilimumab	Nivolumab in combination with ipilimumab	N/A
Comparator(s)	Pazopanib Sunitinib	Pazopanib Sunitinib	N/A
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY.	Incremental cost per QALY gained analysis	N/A
Key: N/A, not applicable; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.			

B.1.2. Description of the technology being appraised

A description of NIVO+IPI is presented in Table 2. The draft summary of product characteristics (SmPC) is presented in Appendix C. The European Public Assessment Report (EPAR) should be available Q3 2018.

Table 2: Technology being appraised

UK approved name and brand name	Nivolumab + ipilimumab (Opdivo® + Yervoy®)
Mechanism of action	CTLA-4 and PD-1 are immune checkpoints involved in T-cell differentiation and function: • PD-1 is specifically involved in inhibiting T-cell destruction of healthy 'self-cells' at the effector (later) stage of the immune response. – Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 to limit the activity of T-cells at the tumour site. • CTLA-4 is specifically involved in inhibiting constant T-cell production to avoid 'self-damage' in the priming and activation (early) stage of the immune response. – This pathway 'switches off' the immune response to tumour antigens, stopping production of activated T-cells in human malignancy. Nivolumab and ipilimumab are both fully human, monoclonal immunoglobulin antibodies (IgG4 and IgG1k HuMab, respectively) that act as checkpoint inhibitors of PD-1 and CTLA-4, respectively, at their distinct yet complementary positions within the T-cell response pathway: • Nivolumab stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour. • Ipilimumab stops the immune response from being 'switched off', thus allowing the production of active T-cells to continue and increasing the number of activated T-cells surrounding the tumour. NIVO+IPI therefore potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell); this results in destruction of the tumour through pre-existing, intrinsic processes.
Marketing authorisation	An application was filed on 7 November 2017 to the EMA to allow nivolumab and ipilimumab to be used in combination with each other for the treatment of untreated, advanced RCC in adults with intermediate- or poor-risk disease. CHMP opinion and MA are expected in 2018
Indications and any restriction(s) as described in the summary of product	The anticipated indication of interest within this submission is: "for the treatment of adult patients with intermediate-/poor-risk advanced renal cell carcinoma"

characteristics (SmPC)	NIVO+IPI is also indicated in the UK and Europe for the treatment of advanced (unresectable or metastatic) melanoma in adults. Nivolumab monotherapy is licensed for the following indications: • for the treatment of advanced RCC after prior therapy in adults • for the treatment of advanced (unresectable or metastatic) melanoma • for the treatment of squamous NSCLC after previous chemotherapy • for the treatment of relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin • for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • for the treatment of locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy Ipilimumab monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma.
Method of administration and dosage	Intravenous infusion. Nivolumab 3mg/kg plus ipilimumab 1mg/kg q3w for 4 doses followed by nivolumab 3mg/kg q2w. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. In the CheckMate 214 study, median time on treatment was 7.9 months, and patients are thought unlikely to receive treatment for more than 5-years (see Section B.2.10 and B.3.4)
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	£1,097.00 per 100mg vial; £439.00 per 40mg vial. [redacted] Undiscounted estimate from deterministic base case economic analysis, as reported in Section A.12.
Patient access scheme (if applicable)	There is a simple discount patient access scheme for nivolumab and ipilimumab approved by the Department of Health that is applicable to this appraisal.

Key: ASCT, autologous stem cell transplant; EMA, European Medicines Agency; CHMP, Committee for Medicinal Products for Human Use; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MA, marketing authorisation; NIVO+IPI, nivolumab + ipilimumab; NSCLC, non-small cell lung cancer; PD-1, programmed death receptor-1; q2w, every 2 weeks; q3w, every 3 weeks; RCC, renal cell carcinoma; SmPC, Summary of Product Characteristics.

B.1.3. Health condition and position of the technology in the treatment pathway

Kidney cancer is the seventh most common cancer in the UK, but it is still relatively rare, accounting for only 3% of all new cancer cases in 2014.[1] Renal cell carcinoma (RCC), where cancerous cells develop within the epithelia of the renal tubules, is the most common type of kidney cancer, responsible for approximately 80% of all cases of kidney cancer diagnosed in the UK.[2, 3] Metastatic disease (Stage IV) is found in 30% of all patients at diagnosis[4-8] with around 75% of renal cancer being of the clear-cell histology.[9]

Over half of all kidney cancer cases are diagnosed in people aged 70 and over, with men up to twice as likely to develop RCC than women. Many environmental and clinical factors are implicated in the aetiology of RCC, with the most common risk factors including smoking and obesity; an estimated 42% of kidney cancers in the UK are attributed to these factors.[2]

Multiple scoring systems are available to characterise prognosis in RCC. Two of the most commonly used in advanced RCC are the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC), each of which categorises patients as favourable-, intermediate- or poor-risk based on how many adverse prognostic factors are present.[10, 11] While both scoring systems have parameters of Karnofsky Performance Status (KPS), time from diagnosis to treatment, haemoglobin value and corrected calcium concentration, the IMDC scoring system also includes absolute neutrophil count and platelet count, and only the MSKCC scoring system includes lactate dehydrogenase levels.[11, 12] A summary of prognostic factors assessed in the IMDC and MSKCC scoring systems is presented in Table 3.

Both scoring systems are used in clinical practice, and both demonstrate good concordance.[13] However, as IMDC is a newer prognostic tool brought about in the current era of targeted therapies, and is believed to offer more granularity, it is generally preferred by clinicians. According to IMDC and based on CheckMate 214 patients, approximately 24% of patients are in the favourable-risk group, 58% are in the intermediate-risk group, and 18% are in the poor-risk group.[14]

Table 3: Summary of IMDC and MSKCC scoring systems

Prognostic factor	MSKCC[10]	IMDC[11]
Time from diagnosis to systemic treatment <1 year	Yes	Yes
Haemoglobin < LLN[a]	Yes	Yes
Calcium >10mg/dL (>2.5 mmol/L)	Yes	Yes
LDH > 1.5x ULN[b]	Yes	No
Karnofsky performance status <80%	Yes	Yes
Absolute neutrophil count > ULN	No	Yes
Platelet count > ULN	No	Yes
Number of adverse factors for:		
Favourable-risk	0	0
Intermediate-risk	≤2	≤2
Poor-risk	≥3	≥3

Key: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LDH, lactate dehydrogenase; LLN, lower limit of normal; MSKCC, Memorial Sloan-Kettering Cancer Center; ULN, upper limit of normal
Notes: [a], 13.5-17.5 g/dL for men and 12.0-15.5g/dL for women; [b], normal of 140 U/L

Metastatic RCC is a life-threatening condition with a 5-year survival rate of only 10–15%.[15] Furthermore, survival has been shown to decrease with increasing adverse prognostic factors. In a population-based study investigating survival differences of patients treated with first-line vascular endothelial growth factor (VEGF)-targeted therapy based on prognostic risk, a median overall survival (OS) of 43.2 months was seen in IMDC favourable-risk patients; this halved to 22.5 months for intermediate-risk patients, and was further reduced to just 7.8 months in poor-risk patients.[13]

Detection of suspected RCC is often incidental as the disease can be relatively asymptomatic in the early stages.[16] Patients that do have symptoms usually present with pain or discomfort in the upper abdomen or back (flank pain), gross haematuria and a palpable lump or mass in the kidney area; these make up the classic triad of kidney cancer symptoms.[2, 16] The altered immune response caused by the tumour may also result in symptoms such as hypercalcaemia, fever and weight loss.[2, 16] Patients with metastatic disease may experience further physical symptoms based on the location of their metastases.

The symptoms of advanced disease coupled with the psychological impact of suffering from a life-threatening disease can significantly impact individual patients'

everyday lives and overall well-being.[17-20] Advanced RCC impacts on all domains of patient health-related quality of life (HRQL) including physical and psychosocial function.[18] Importantly, treatment-related adverse events (TRAEs) from systemic therapies used in the management plan can further reduce HRQL.[17, 18] In addition to patient burden, advanced RCC can also present a 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.[18, 21-23]

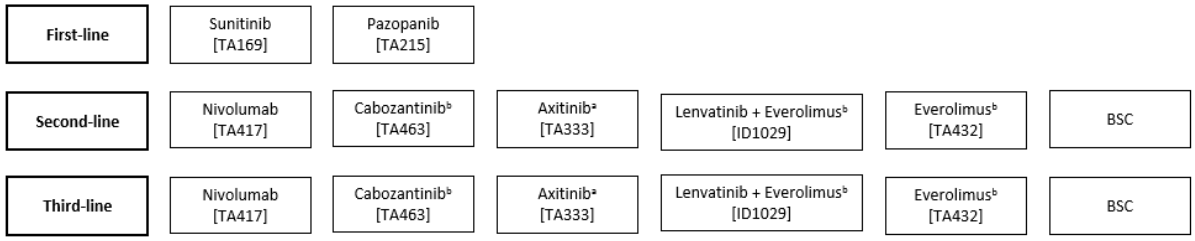
Clinical pathway of care

The National Institute for Health and Care Excellence (NICE) currently recommends sunitinib (Sutent®) and pazopanib (Votrient®) for use in patients with untreated, advanced RCC who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.[24-26] Despite significant progression-free survival (PFS) benefits demonstrated for both sunitinib and pazopanib in regulatory Phase III trials (compared with interferon-α [IFN-α] or placebo, respectively),[27, 28] no trial has shown a significant OS benefit in either drug.

Although IFN-α and high-dose interleukin-2 (IL-2) are alternative treatment options, these are used in very few, very select patients due to significant toxicities. Indeed, clinical consultation confirmed that no one in the UK is currently treated with IFN-α and that only around 1% of treated metastatic RCC (mRCC) patients in the UK currently receive IL-2 in a single cancer centre. It is used either pre- or post-first-line VEGF receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy for highly selected patients.[29]

Current first-line treatments are therefore restricted to VEGFR TKI systemic agents (sunitinib and pazopanib) with no proven OS benefit and the possibility of significant toxicity with cardiovascular complications, gastrointestinal (GI) complications, dermatological reactions, and laboratory abnormalities associated with this class of treatment.[30, 31] There is a clear need for alternative treatment modalities to improve physician and patient choice and potentially improve the life expectancy of patients. Current treatment options for advanced RCC in the NHS are presented in Figure 1.

Figure 1: Current treatment options in NHS England



Key: BSC, best supportive care; IL-2, interleukin-2; TA, technology appraisal; VEGF, vascular endothelial growth factor.
Notes: [a], After failure of treatment with a first-line VEGF-targeted therapy; [b], after prior VEGF-targeted therapy. IL-2 is omitted from the figure due to limited use in the UK.

NIVO+IPI is an innovative immunotherapy combination treatment with a different mode of action, offering an alternative first-line treatment option and the potential for long-term survival to patients with previously untreated, intermediate-/poor-risk advanced RCC. Based on the data from CheckMate 214 (see Section B.2), the European Association of Urology (EAU) guidelines for the treatment of first-line metastatic RCC have been updated and now recommend NIVO+IPI as the standard of care in intermediate-/poor-risk patients with alternative agents (including sunitinib and pazopanib) being considered when NIVO+IPI is not safe or feasible.[32]

If similarly recommended by NICE, after first-line treatment with NIVO+IPI, it is anticipated that patients will go on to receive either cabozantinib or axitinib in the second-line setting, although some clinicians may want to consider sunitinib or pazopanib after first-line NIVO+IPI, if permitted by NICE to do so.[29]

B.1.4. Equality considerations

No equality considerations have been identified or are anticipated.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The systematic literature review (SLR) identified one randomised controlled trial (RCT) that provided evidence on the clinical benefits of the NIVO+IPI regimen, the Phase III CheckMate 214 trial. Supportive evidence is provided by the Phase I CheckMate 016 study. Both studies are summarised in Table 4.

Table 4: Clinical effectiveness evidence

	CheckMate 214 (NCT02231749)					**CheckMate 016 (NCT01472081)**				
Study design	Phase III, randomised, open-label					Phase I, non-randomised, open-label				
Population	Adults (≥18 years) with previously untreated advanced or metastatic RCC with a clear-cell component The primary analysis set comprised intermediate- and poor-risk patients.					Adults (≥18 years) with previously treated or treatment naïve advanced or metastatic RCC				
Intervention(s)	Nivolumab 3mg/kg IV combined with ipilimumab 1mg/kg IV Q3W for 4 doses then nivolumab 3mg/kg IV Q2W					Nivolumab 3mg/kg IV combined with ipilimumab 1mg/kg IV Q3W for 4 doses then nivolumab 3mg/kg IV Q2W Nivolumab 1mg/kg IV combined with ipilimumab 3mg/kg IV Q3W for 4 doses then nivolumab 3mg/kg IV Q2W Nivolumab 3mg/kg IV combined with ipilimumab 3mg/kg IV q3W for 4 doses then nivolumab 3mg/kg Q2W [a] Nivolumab plus sunitinib [a] Nivolumab plus pazopanib [a]				
Comparator(s)	Sunitinib 50mg PO once daily for 4 weeks followed by 2 weeks off, continuously					N/A				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No		No			No	X
Rationale for use/non-use in the model	Pivotal trial supporting this indication					Supportive evidence for the intervention of interest within this indication				

	CheckMate 214 (NCT02231749)	CheckMate 016 (NCT01472081)
Reported outcomes specified in the decision problem (Outcomes in bold are incorporated into the model)	In intermediate- and poor-risk patients: • **OS** • **PFS** • **Response rates** In any-risk patients: • **AEs** • **HRQL**	• OS • PFS • Response rates • AEs
All other reported outcomes (Outcomes in bold are incorporated into the model)	In intermediate- and poor-risk patients: • PD-L1 tumour expression In any-risk patients: • OS • PFS • Response rates • PD-L1 tumour expression	• PK assessments
Key: AE, adverse event; HRQL, health-related quality of life; IV, intravenous; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death receptor ligand-1; PK, pharmacokinetic; PO, orally; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma. **Notes:** [a], Arms were closed due to dose-limiting toxicity.		

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. CheckMate 214

Study design

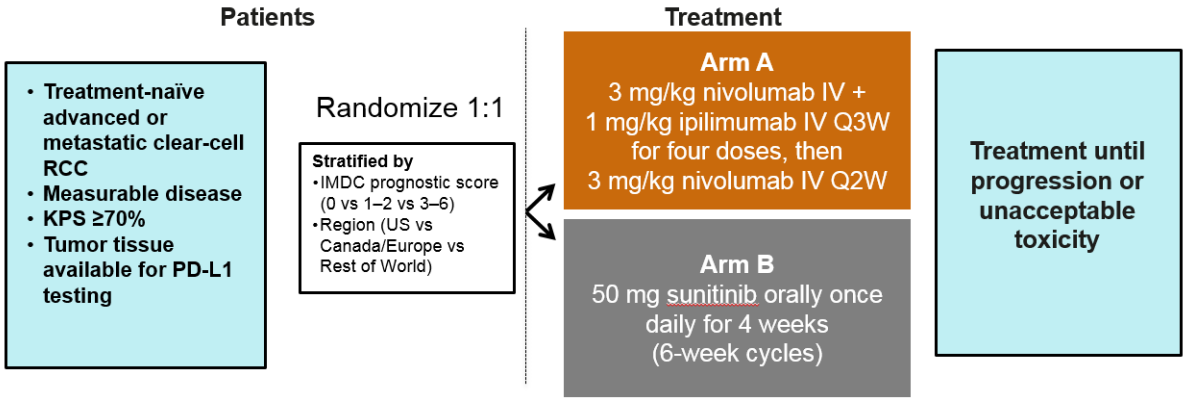
CheckMate 214 is a Phase III, randomised, open-label study of nivolumab combined with ipilimumab (i.e. NIVO+IPI) versus sunitinib monotherapy in patients with previously untreated, advanced RCC with a clear-cell component. CheckMate 214 is the pivotal trial supporting this indication, providing a median patient follow-up of 25.2 months, and was the key trial used in regulatory submission. The trial was conducted at 184 sites in 28 countries including six sites in the UK, of which four were in England. Patients were randomised in a 1:1 ratio to receive treatment with NIVO+IPI or sunitinib. Randomisation was stratified by IMDC prognostic score and region.[14]

To be eligible for inclusion in the study, patients must have had histological confirmation of advanced or metastatic RCC with a clear-cell component. The trial included treatment-naïve patients, although one prior therapy was allowed if this did not include an agent that targets VEGF or VEGFRs and if recurrence of disease occurred at least 6 months after the last dose of therapy. Patients were categorised as favourable-, intermediate- or poor-risk at registration. To be eligible for the intermediate-/poor-risk cohort, at least one of the six prognostic factors as per the IMDC criteria (presented in Section B.1.3) had to be present.[33]

The study consisted of three phases: screening, treatment and follow-up.[33] Patients were assessed for response by CT or MRI, beginning 12 weeks from randomisation and continuing every 6 weeks for the first 13 months, and then every 12 weeks until progression or treatment discontinuation.[33] There are three co-primary endpoints of the study: independent radiology review committee (IRRC)-assessed objective response rate (ORR), PFS in intermediate- and poor-risk patients, and OS in intermediate- and poor-risk patients.[14] This intermediate- and poor-risk primary analysis set constitutes a population with the highest unmet medical need and most severe prognosis.

A study design schematic diagram is presented in Figure 2.

Figure 2: Study design schematic



Key: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenous; KPS, Karnofsky Performance Status; PD-L1, programmed death receptor ligand-1; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma.
Source: Escudier *et al.* 2017[14]

Secondary endpoints included ORR, PFS and OS in any-risk patients and adverse events (AEs).[14] Outcomes by PD-L1 expression and HRQL were key exploratory endpoints. HRQL was assessed by the Functional Assessment of Cancer Therapy-General (FACT-G), the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) and the EQ-5D®.[14, 33] Full details, including scoring methods, of the HRQL tools used in this study are presented in Appendix L.

Of note, patients could continue treatment beyond initial Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression (where progression is assessed 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 response and/or stable disease. Patients treated beyond initial RECIST-defined progression discontinued study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumour burden volume from time of initial progression.

A summary of the methodology for CheckMate 214 is presented in Table 5.

Table 5: Summary of CheckMate 214 methodology

Trial name	**CheckMate 214**
Location	184 sites in 28 countries including the US, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Republic of Korea, Mexico, the Netherlands, Poland, Spain, Sweden, Taiwan, Turkey and the UK.
Trial design	A multinational, randomised, open-label, active-controlled, Phase III trial Patients were randomised in a 1:1 ratio through an IVRS. Randomisation was stratified by IMDC prognostic score (0 vs. 1–2 vs. 3–6) and region (US vs. Canada and Europe vs. rest of the world).
Eligibility criteria for participants	Men and women aged ≥18 years were included if they met the following criteria: • Histological confirmation of RCC with a clear-cell component • Advanced or metastatic RCC • Signed written informed consent

	• No prior systemic therapy for RCC with the following exception: – One prior adjuvant or neo-adjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGFRs and if recurrence occurred at least 6 months after the last dose of therapy • KPS of at least 70% • Measurable disease as per RECIST v1.1 • Favourable-, intermediate- or poor-risk disease as per the IMDC criteria • Women of childbearing potential must have a negative pregnancy test, must not be breastfeeding, and must agree to follow instructions for methods of contraception. Patients were excluded from the study if they met any of the following criteria: • Any history of or current CNS metastases • Prior systemic treatment with VEGF- or VEGFR-targeted therapy • Prior treated with an anti-PD-1, anti-PD-L1, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • Any active or recent history of a known or suspected autoimmune disease • Any condition requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days prior to first dose of study drug • Uncontrolled adrenal insufficiency • Cardiovascular conditions including ongoing, symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation or prolonged QT interval, poorly controlled hypertension or history or cerebrovascular accident including TIA within the past 12 months • History of DVT, pulmonary embolism, abdominal fistula, GI perforation or intra-abdominal abscess within the past 6 months • Serious non-healing wound or ulcer • Evidence of active bleeding or bleeding susceptibility; or medically significant haemorrhage within prior 30 days • Any requirement for anti-coagulation, except for low molecular weight heparin • Prior malignancy active within the previous 3 years • Know history or testing positive for HIV or AIDS; any positive test for hepatitis B or hepatitis C • Known medical condition that would increase the risk associated with study participation • Major surgery or anti-cancer therapy less than 28 days prior to the first dose of study drug • Presence of any toxicities attributed to prior anti-cancer therapy that have not resolved to Grade 1 • Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors

	• Impairment of GI function or disease that may significantly alter the absorption of sunitinib
Settings and locations where the data were collected	An independent DMC was set up to provide independent oversight of safety, efficacy and study conduct. The DMC reviewed all data at the planned interim analyses and also provided recommendations to the Sponsor regarding continuation of the study. Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality.
Trial drugs	Nivolumab 3mg/kg IV combined with ipilimumab 1mg/kg IV Q3W for 4 doses then nivolumab 3mg/kg IV Q2W Sunitinib 50mg PO once daily for 4 weeks followed by 2 weeks off, continuously Treatment continued until progression or unacceptable toxicity.
Permitted and disallowed concomitant medication	The following medications are prohibited during the study: • Immunosuppressive agents (except to treat a drug-related adverse event) • Systemic corticosteroids >10mg daily prednisone equivalent • Any concurrent antineoplastic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, surgical resection except for palliative surgical resection, or standard or investigational agents for treatment of cancer) Supportive care for disease-related symptoms may be offered to all patients in the trial. Palliative radiation therapy and palliative surgical resection are permitted if the following criteria are met: • The patient will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression • The case is discussed with the manufacturer's medical monitor Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids. Physiological replacement doses of systemic corticosteroids are permitted, even if >10mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
Primary outcomes (including scoring methods and timings of assessments)	• PFS in intermediate- and poor-risk patients: – Primary definition (PFS truncated at subsequent therapy): defined as time between the date of randomisation and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Subsequent therapy included anticancer therapy, tumour-directed radiotherapy, or tumour-directed surgery. Patients who died without a reported progression were considered to have progressed on the date of their death. – Secondary definition: defined as the time between the date of randomisation and the first date of documented progression, as

	determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Patients who died without a reported progression were considered to have progressed on the date of their death. • OS in intermediate- and poor-risk patients, defined as the time from randomisation to the date of death from any cause • ORR in intermediate- and poor-risk patients, defined as the proportion of randomised patients who achieved a best response of CR or PR, based on IRRC assessment (as per RECIST v1.1)
Other outcomes used in the economic model/specified in the scope	• PFS in all randomised patients, as defined above • OS in all randomised patients, as defined above • ORR in all randomised patients, defined as the proportion of randomised patients who achieve a best response of CR or PR, based on IRRC assessment (as per RECIST v1.1) • Safety and tolerability, measured by the incidence of AEs, SAEs, deaths and laboratory abnormalities in all randomised patients, graded using the NCI CTCAE v4.0 • HRQL in all randomised patients, assessed by FACT-G and FKSI-19. Global health status was assessed by EQ-5D instrument.
Pre-planned subgroups	OS and PFS were estimated in the two treatment arms among patients with favourable risk per IMDC prognostic criteria.
Key: AE, adverse event; AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DMC, data monitoring committee; DVT, deep vein thrombosis; FACT-G, Functional Assessment of Cancer Therapy – General; FKSI-19, Functional Assessment of Cancer Therapy – Kidney Symptom Index; GI, gastrointestinal; HIV, human immunodeficiency virus, HRQL, health-related quality of life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRRC, independent radiology review committee; IV, intravenous; IVRS, interactive voice response system; KPS, Karnofsky Performance Status; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; PFS, progression-free survival; PO, orally; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; RCC, renal cell carcinoma; SAE, serious adverse event; TIA, transient ischaemic attack; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. **Source:** Escudier *et al.* 2017[14]; CheckMate 214 CSR[33]	

Baseline characteristics

Baseline characteristics for the intermediate-/poor-risk patients are presented in Table 6, alongside the total population.

Among intermediate-/poor-risk patients, baseline demographic and disease characteristics were well balanced between treatment groups. Approximately 80% of patients had two or more disease sites, with the most common site of metastasis being the lung (70% of patients), followed by the lymphatic system. Of patients who had a baseline tumour tissue sample quantifiable for PD-L1 testing (384 of 425 in

NIVO+IPI arm; 392 of 422 in sunitinib arm), 26% of NIVO+IPI patients and 29% of sunitinib patients were positive for PD-L1 expression (≥1%) at baseline.[14]

Consistent with the inclusion criteria, most patients in both groups had received no prior anticancer therapy. In each treatment group, 0.5% of patients received prior systemic chemotherapy in the adjuvant setting, and 0.2% of patients in the NIVO+IPI group received prior systemic chemotherapy in the neo-adjuvant setting.[33]

Table 6: Baseline characteristics of all patients, CheckMate 214

	Intermediate-/poor-risk patients (N=847)		**Total population (N=1,096)**	
	NIVO+IPI (n=425)	Sunitinib (n=422)	NIVO+IPI (n=550)	Sunitinib (n=546)
Median age, years (range)	62 [redacted]	61 [redacted]	62 [redacted]	62 [redacted]
Male, n (%)	[redacted](74)	[redacted] (71)	413 (75)	395 (72)
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
KPS, n (%):				
100	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]
<70	[redacted]	[redacted]	[redacted]	[redacted]
IMDC prognostic score[a], %:				
Favourable (0)	0	0	23	23
Intermediate (1–2)	79	79	61	61
Poor (3–6)	21	21	17	16
PD-L1 expression, n (%):	N=384	N=392	N=499	N=503
<1%	284 (74)	278 (71)	384 (77)	377 (75)
≥1%	100 (26)	114 (29)	115 (23)	126 (25)
No. of sites with ≥1 target/non-target lesion:				
1	90 (21)	84 (20)	123 (22)	118 (22)
≥2	335 (79)	338 (80)	427 (78)	428 (78)

	Intermediate-/poor-risk patients (N=847)		Total population (N=1,096)	
	NIVO+IPI (n=425)	Sunitinib (n=422)	NIVO+IPI (n=550)	Sunitinib (n=546)
Most common sites of metastasis, n (%):				
Lung	293 (69)	295 (70)	380 (69)	371 (68)
Lymph node	191 (45)	215 (51)	248 (45)	268 (49)
Liver	89 (21)	89 (21)	99 (18)	109 (20)
Bone	85 (20)	89 (21)	99 (18)	104 (19)
Prior systemic therapy, n (%):				
Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]
Neo-adjuvant	[redacted]	[redacted]	[redacted]	[redacted]
Prior surgery, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, n (%)	52 (12.2)	52 (12.3)	63 (11.5)	70 (12.8)

Key: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IVRS, interactive voice response system; KPS, Karnofsky Performance Score; NIVO+IPI, nivolumab + ipilimumab; PD-L1, programmed death receptor ligand-1.
Notes: [a], IVRS recorded.
Source: Escudier *et al.* 2017[14]; CheckMate 214 CSR[33]

B.2.3.2. CheckMate 016

CheckMate 016 is a Phase I, non-randomised, open-label study investigating various combinations of nivolumab-based therapy in patients with advanced RCC with a clear-cell component and a KPS ≥80%.[34] The arms of interest to this submission, and for which results are reported, were nivolumab 1mg/kg plus ipilimumab 3mg/kg (N1I3) and nivolumab 3mg/kg plus ipilimumab 1mg/kg (N3I1): this arm (N3I1) reflects the marketing application. A total of 47 patients were assigned to each study arm (N1I3 and N3I1), and most patients were in the favourable-risk (45%) or intermediate-risk (49%) categories based on the MSKCC prognostic score. Approximately 50% of patients in each arm were treatment-naïve (53% of the N3I1 arm and 48% of the N1I3 arm). The primary outcome of the study was to assess the safety and tolerability of NIVO+IPI in order to determine the maximum tolerated dose. Data presented in this submission are based on a median follow-up of 37.7 months in the N3I1 arm, after the latest analysis at June 2017 data cut-off. Full

details on study methodology, statistical analysis, quality assessment and participant flow are provided in Appendix M.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The hypotheses and associated statistical analysis methods adopted in CheckMate 214 are presented in Table 7.

Statistical analysis plans (SAPs) were developed and approved prior to study initiation. The primary efficacy analyses were conducted on the intermediate- and poor-risk patients, as defined in Section B.2.3. Of note, the overall alpha for this study's primary endpoints is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS. Secondary efficacy analyses were conducted on all randomised patients of any risk category. PFS and OS were subject to hierarchical testing: first testing in intermediate-/poor-risk patients, followed by testing in all randomised patients, if significant. Exploratory analyses of the efficacy endpoints were conducted on favourable-risk patients. The primary dataset for safety analyses was the total (all treated) patients, defined as all patients (of any risk category) who received any dose of study therapy. Standard censoring rules applied to missing data. The following censoring rules were applied to both the primary and secondary definitions of PFS:

- Patients who did not progress or died were censored on the date of the last evaluable tumour assessment.
- Patients who did not have any on-study tumour assessments or died were censored on the date of randomisation.

These additional censoring rules applied to only the primary definition of PFS:

- Patients who received subsequent systemic anti-cancer therapy prior to documented progression were censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy.
- Patients who did not have a documented progression and received subsequent anticancer therapy were censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy.

Results presented within this submission are based on a clinical database lock of 7 August 2017.

The number of patients randomised to treatment arms is provided in Appendix D alongside a Consolidated Standards Of Reporting Trials (CONSORT) diagram of participant flow.

Table 7: Summary of statistical analyses, CheckMate 214

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with NIVO+IPI will improve PFS, OS, ORR, or all three outcomes compared to sunitinib monotherapy in patients with previously untreated metastatic RCC.	The overall alpha for this study's primary endpoints is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS with at least 80% power and 0.04 to evaluate OS with 90% power, accounting for two formal interim analyses to assess efficacy. At the time of database lock, the number of deaths was half of the total OS events, so an adjusted alpha of 0.002 was applied (to provide 98% CI). The first interim analysis of OS was planned at the time of final ORR and PFS analysis. At this time, it was expected to observe approximately 465 PFS events and 330 OS events (52% of the targeted OS events for final analysis) in the intermediate-/poor-risk patients. The stopping boundaries at the interim OS analyses were derived based on the number of deaths using O'Brien and Fleming α-spending function. A hierarchical testing procedure was used for secondary endpoints so that the overall experiment-wise Type 1 error rate was 0.05. The formal testing of PFS based on	It was estimated that approximately 1,070 previously untreated metastatic RCC patients would be randomised in a 1:1 ratio, including among them 820 patients with intermediate-/poor-risk and 250 with favourable-risk as per IMDC. Assuming a 21% screen failure rate, it was estimated that approximately 1,355 patients would be enrolled. For PFS, 583 events were required among the randomised intermediate-/poor-risk patients for a two-sided experiment-wise α=0.01 log-rank test, to show a statistically significant difference in PFS between the treatment arms with at least 90% power when the true HR of the experimental arm to control arm is 0.73. The HR of 0.73 is equivalent to demonstrating a 37.8% improvement in median PFS. Approximately 639 OS events are required to provide 90% power to detect a HR of 0.766 with an overall Type 1 error of 0.04 (two-sided). The HR of 0.766 corresponds to a 30.6% increase in the median OS. A HR of 0.846 or less, which corresponds to a 3.6	Patients who did not progress or die will be censored on the date of their last evaluable tumour assessment. Patients who did not have any on-study tumour assessments and did not die will be censored on their date of randomisation. Patients who receive subsequent systemic anti-cancer therapy prior to documented progression will be censored at the date of the last tumour assessment prior to the initiation of the new therapy.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	IRRC assessment, at a two-sided 0.01 significance level, among all randomised patients will take place if PFS based on IRRC assessment among intermediate-/poor-risk patients is statistically significant. Likewise, the testing of OS, at a two-sided 0.04 significance level, among all randomised patients will take place only if OS intermediate-/poor-risk patients are statistically significant. The detail of the testing procedure will be specified in the SAP. Primary endpoints were estimated via the KM product limit method. Two-sided 95% CI for the median PFS and OS were computed for each randomised arm. HR and corresponding two-sided 99% CI were estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors. Response rate was estimated by Clopper–Pearson method with a two-sided 95% CI.	months or greater improvement in median OS, would result in a statistically significant improvement in OS for the experimental arm at the final OS analysis.	

Key: CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; IRRC, Immune Related Response Criteria; KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SAP, statistical analysis plan.
Source: CheckMate 214 CSR[33]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A summary of quality assessment for CheckMate 214 is presented in Table 8 with full details in Appendix D.

The study 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. Baseline demographics and disease characteristics between treatment arms were well balanced, with no key differences between groups. The most common reason for study withdrawal was disease progression, which is accounted for within the 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 endpoints of OS, PFS and ORR are not subjectively assessed endpoints, and lack of blinding was therefore not thought to have a considerable effect on the outcome of the study.

Disease evaluation and safety evaluation methods are consistent with other studies of RCC therapy, and 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 B.2.13), patients were allowed to receive treatment beyond RECIST-defined progression to better reflect clinical practice. Indeed, the trial is thought to reflect routine clinical practice in England with respect to population, comparator choice, treatment administration and outcomes being assessed. Patients with previously untreated, advanced RCC were eligible for inclusion in the study, a population of direct relevance to the decision problem. Furthermore, the trial provides direct head-to-head evidence compared to sunitinib, the current standard of care in NHS England. It is also important to note that alongside clinical efficacy and safety outcomes, HRQL outcomes were also measured, as requested by reimbursement agencies.

Table 8: Quality assessment for CheckMate 214

CheckMate 214	
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, open-label study
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
Source: CheckMate 214 CSR.[33]	

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. CheckMate 214

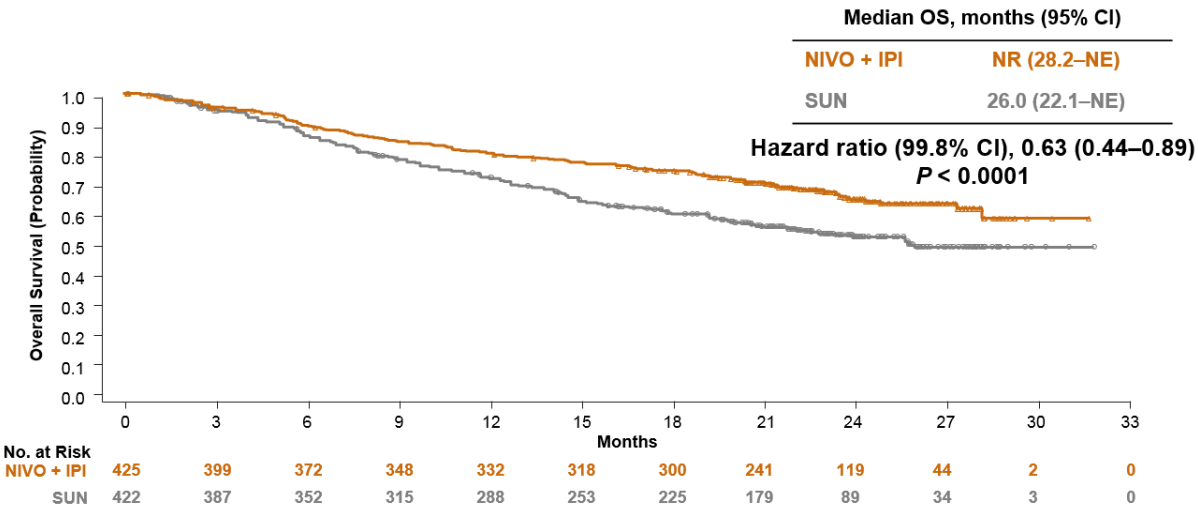
OS in intermediate-/poor-risk patients (co-primary outcome)

After a median follow-up of 25.2 months, deaths had occurred in 140 patients (32.9%) in the NIVO+IPI group and 188 patients (44.5%) in the sunitinib group.[33] Median OS was not reached (NR) (95% confidence interval [CI]: 28.2, not evaluable [NE]) in the NIVO+IPI group and was 26.0 months (95% CI: 22.1, NE) in the sunitinib group.[14] The corresponding hazard ratio (HR) for death from any cause confirmed a superior OS benefit in favour of NIVO+IPI: 0.63 (99.8% CI: 0.44, 0.89; p<0.001).

The 6-month OS rate was 89.5% and 86.2% in the NIVO+IPI and sunitinib groups, respectively, and the 12-month rate was 80.1% and 72.1%, respectively. Based on Kaplan–Meier (KM) estimates, the 18-month rate was 74% and 60%, respectively, and the 24-month rate was 65% and 53%, respectively.

The KM curve for OS is presented in Figure 3.

Figure 3: Kaplan–Meier curve for OS in CheckMate 214, intermediate-/poor-risk patients



Key: CI, confidence interval; NE, not estimable; NIVO+IPI, nivolumab + ipilimumab; NR, not reached; OS, overall survival; SUN, sunitinib.
Source: Escudier *et al*. 2017[14]

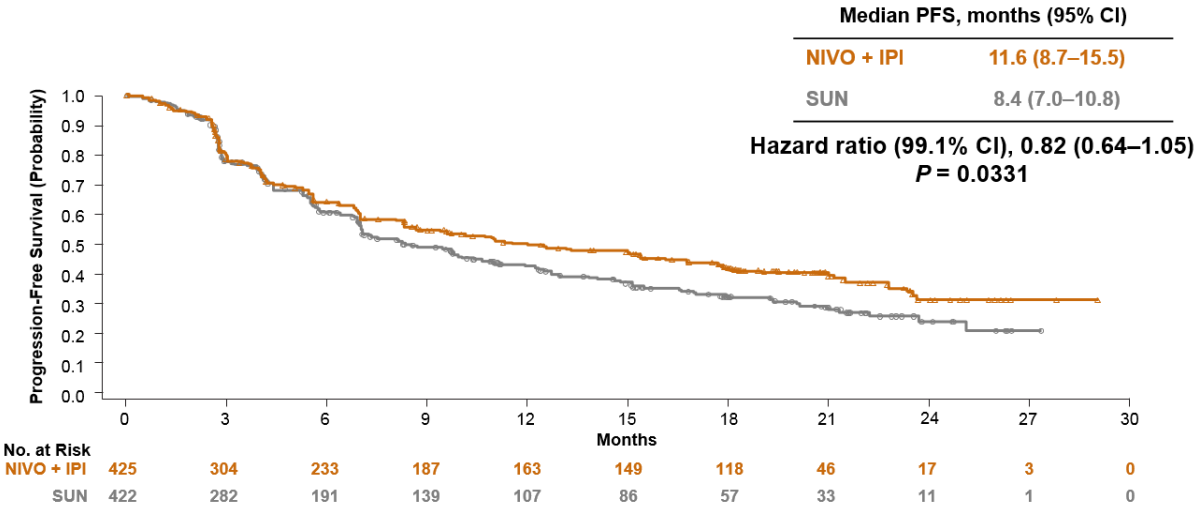
PFS in intermediate-/poor-risk patients (co-primary outcome)

The IRRC-assessed median PFS using RECIST, and censoring for subsequent therapy (primary PFS definition), was 11.6 months (95% CI: 8.75, 15.51) in the NIVO+IPI group and 8.4 months (95% CI: 7.03, 10.81) in the sunitinib group, representing an improvement of 3.2 months, with a corresponding HR of 0.82 (99.1% CI: 0.64, 1.05).[14] Although not statistically significant owing to the weak split alpha value allocation to the PFS endpoint, clinicians consulted believe these data to be clinically meaningful, which will not adversely affect treatment decision making.[29] Importantly, OS, rather than PFS, is considered a more clinically important endpoint, and it should be noted that a different split of the overall alpha could have resulted in a statistically significant result.

A total of [redacted]% and [redacted]% of patients in the NIVO+IPI and sunitinib arms were censored, respectively.[33] The most common reason for censoring was due to receiving subsequent therapy, as seen in [redacted]% of NIVO+IPI patients and [redacted]% of sunitinib patients.[33] The 12-month PFS rate was 49.6% in patients randomised to NIVO+IPI and 42.6% in patients randomised to sunitinib.[33]

The KM curve for PFS is presented in Figure 4.

Figure 4: Kaplan–Meier curve for PFS in CheckMate 214, intermediate-/poor-risk patients



Key: CI, confidence interval; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival; SUN, sunitinib.
Source: Escudier *et al*. 2017[14]

Median PFS when based on the secondary PFS definition (without censoring for subsequent therapy), was similar to the primary definition. In the NIVO+IPI arm, median PFS was 11.0 months (95% CI: 8.34, 15.21) compared to 8.3 months (95% CI: 7.03, 9.79) in the sunitinib arm, resulting in a HR of 0.76 (99.1% CI: 0.60, 0.95; p=0.0014 [exceeding the predefined alpha allocated to PFS]).[33]

Results for PFS per IRRC were concordant when assessed per investigator. Median PFS (primary definition) was [redacted] months for NIVO+IPI and [redacted] months for sunitinib, with a HR of [redacted]. PFS (secondary definition) when assessed per investigator resulted in a HR of [redacted].[33]

ORR in intermediate-/poor-risk patients (co-primary outcome)

The IRRC-assessed ORR using RECIST was 41.6% (95% CI: 36.9, 46.5) in the NIVO+IPI group and 26.5% (95% CI: 22.4, 31.0) in the sunitinib group (p<0.0001). A complete response (CR) was seen in 40 (9.4%) NIVO+IPI patients compared to 5 (1.2) sunitinib patients (p<0.0001).[14] A summary of best overall response is presented in Table 9.

Table 9: Best overall response in CheckMate 214, intermediate-/poor-risk patients

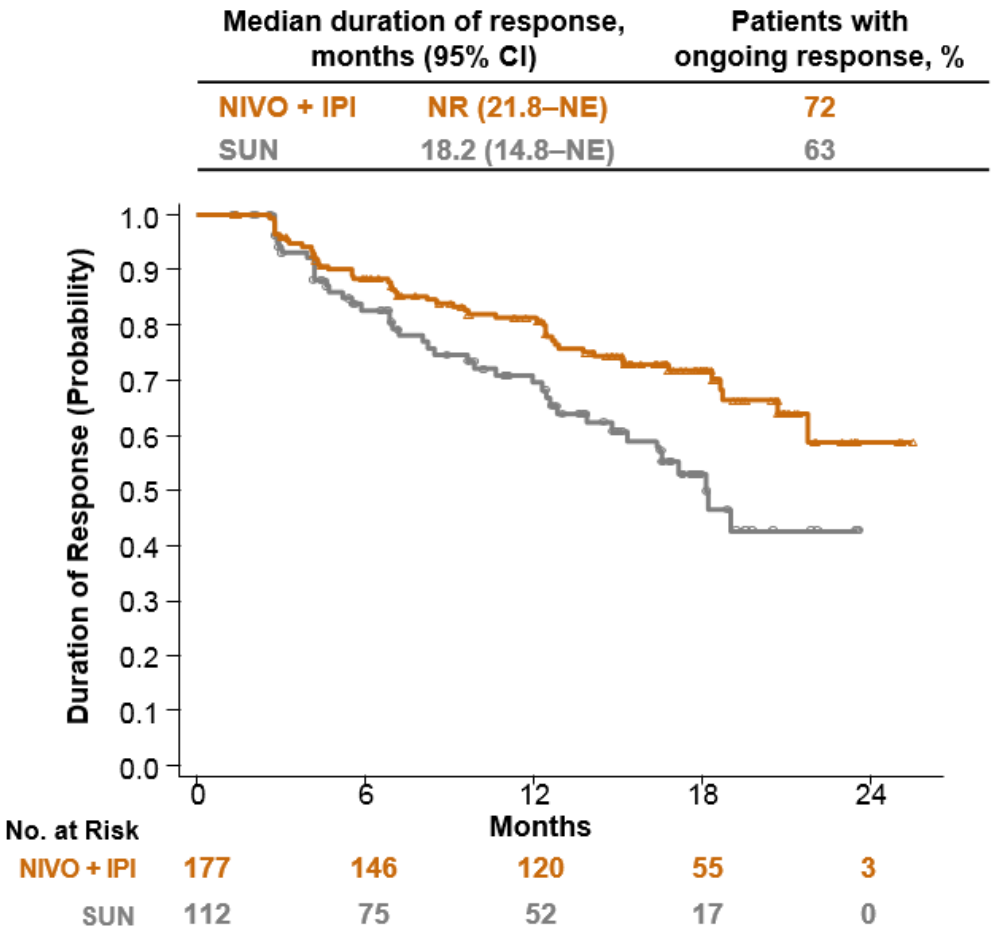
	NIVO+IPI (n=425)	Sunitinib (n=422)
Best overall response (RECIST v1.1)		
Complete response	40 (9.4)	5 (1.2)
Partial response	137 (32.2)	107 (25.4)
Stable disease	133 (31.3)	188 (44.5)
Progressive disease	83 (19.5)	72 (17.1)
Unable to determine	31 (7.3)	50 (11.8)
Not reported	1 (0.2)	0
ORR, n (%)	177 (41.6)	112 (26.5)
95% CI	36.9, 46.5	22.4, 31.0
Difference of ORR, % (95% CI)	[redacted]	
p-value	<0.0001	

Key: CI, confidence interval; NIVO+IPI, nivolumab + ipilimumab; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors.
Source: Escudier *et al*. 2017[14]; CheckMate 214 CSR[33]

Median time to response (TTR) was 2.8 months and 3.0 months in the NIVO+IPI and sunitinib groups, respectively.[33] With a median follow-up of 25.2 months, the median duration of response (DoR) was not reached in the NIVO+IPI group, but was 18.2 months in the sunitinib group, as presented in Figure 5.[14]

At the time of analysis (median follow-up of 25.2 months), 72% of responding patients in the NIVO+IPI group had an ongoing response, compared with 63% of responding patients in the sunitinib group. Therefore, of patients treated with NIVO+IPI, 30.1% of patients can be classified as durable responders, defined as patients who initially responded to treatment and were still responding at the latest available follow-up; a proportion these patients are assumed to have survival similar to the general population. This is further discussed in Section B.3.3.2.

Figure 5: Duration of response in CheckMate 214, intermediate-/poor-risk patients



Key: CI, confidence interval; NE, not evaluable; NIVO+IPI, nivolumab + ipilimumab; NR, not reported; SUN, sunitinib.
Source: Escudier *et al*. 2017[14]

ORR as assessed by the investigator was consistent with ORR as assessed by IRRC. Investigator-assessed ORR was 40.9% (95% CI: 36.2, 45.8) in the NIVO+IPI group and 28.2% (95% CI: 24.0, 32.8) in the sunitinib group.[33]

Secondary outcomes

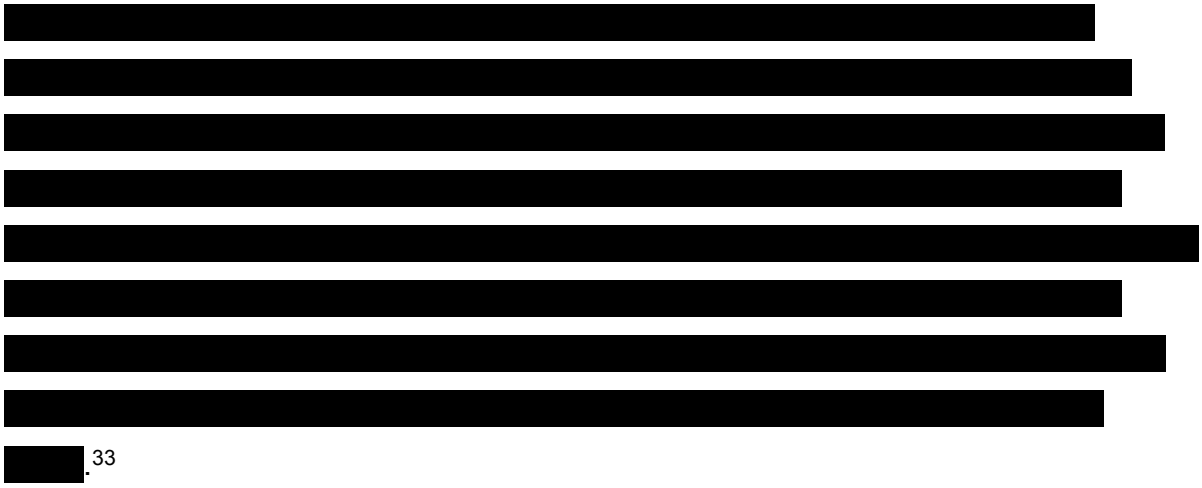
Results of OS, PFS and ORR in the all randomised population are presented in Appendix N.

Overall, the results of the three co-primary endpoints in the all randomised population were consistent with those seen in the intermediate-/poor-risk patients. A significant benefit in OS in favour of NIVO+IPI was observed in this population

compared to sunitinib (HR: 0.68).[14] PFS and ORR were also numerically higher when treated with NIVO+IPI compared to sunitinib.

HRQL

EQ-5D (all randomised patients)



.[33]

.[33]

FACT-G (all randomised patients)

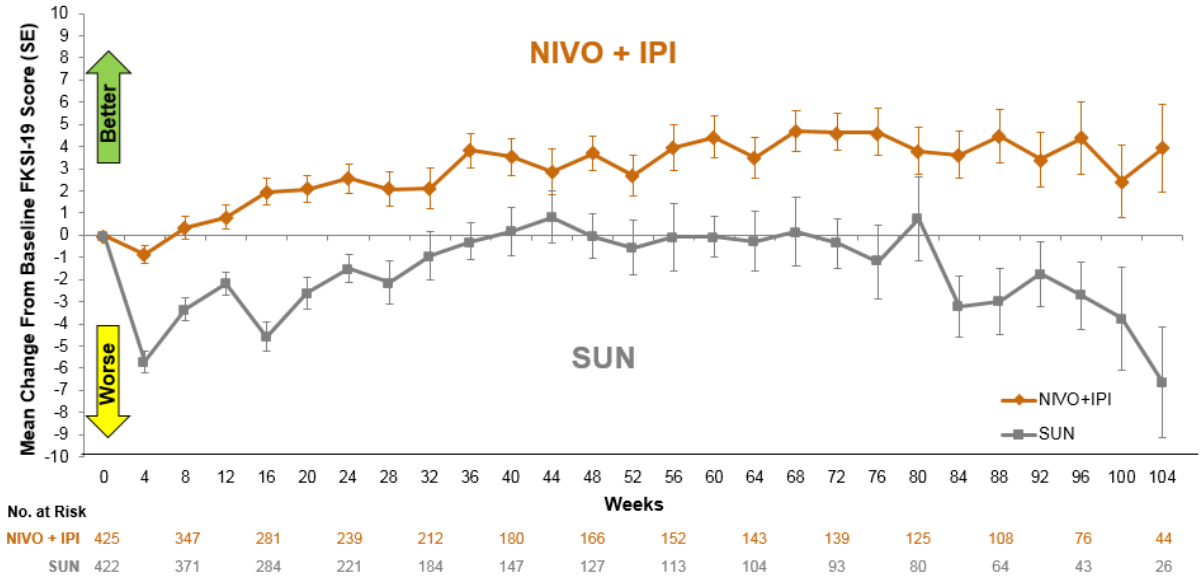
The FACT-G questionnaire was completed by [redacted]% of patients in the NIVO+IPI arm and [redacted]% of patients in the sunitinib arm. Over the first year of follow-up, approximately [redacted]% of the quality of life assessments during NIVO+IPI treatment exceeded baseline values, and [redacted]% of the assessments during sunitinib treatment exceeded baseline values.[33]

FKSI-19 (intermediate-/poor-risk patients)

The FKSI-19 questionnaire, which assesses symptoms of importance to patients with advanced kidney cancer, was completed by over 80% of patients in both arms in the first 6 months of the study.[35] From Week 8 onwards, NIVO+IPI provided a statistically significant improvement in disease symptoms over time; in the sunitinib group, average scores indicated worsening of kidney cancer symptoms.

Change in mean FKSI-19 score is presented in Figure 6.

Figure 6: Mean change in FKSI-19 score in CheckMate 214, intermediate-/poor-risk patients

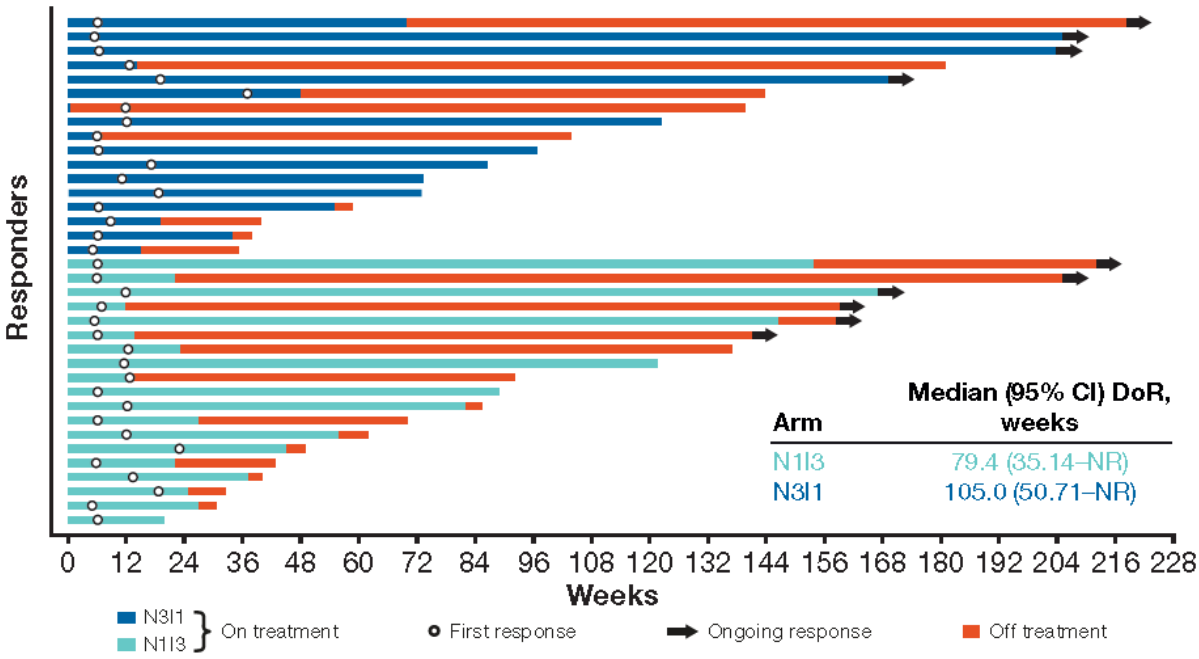


Key: FKSI-19, 19 item Functional Assessment of Cancer Therapy Kidney Symptom Index; NIVO, nivolumab; NIVO+IPI, nivolumab + ipilimumab; SE, standard error; SUN, sunitinib.
Score: Escudier *et al*. 2017[14]

B.2.6.2. CheckMate 016

After a median follow-up of 37.7 months in the N3I1 arm and 36.0 months in the N1I3 arm, ORR was 36.2% in the N3I1 arm and 40.4% in the N1I3 arm.[34] A total of five patients (10.6%) in the N3I1 arm and one patient (2.1%) in the N1I3 arm achieved a CR. An ongoing response was experienced by four of the 17 responders (23.5%) in the N3I1 arm and by six of 19 responders (31.6%) in the N1I3 arm. Median duration of response was 79.4 weeks and 105.0 weeks in the N1I3 and N3I1 arms, respectively, as presented in Figure 7. Of note, of the responding patients at the time of analysis, 60% of patients were off-treatment, suggesting a sustained immunotherapy effect following NIVO+IPI treatment.

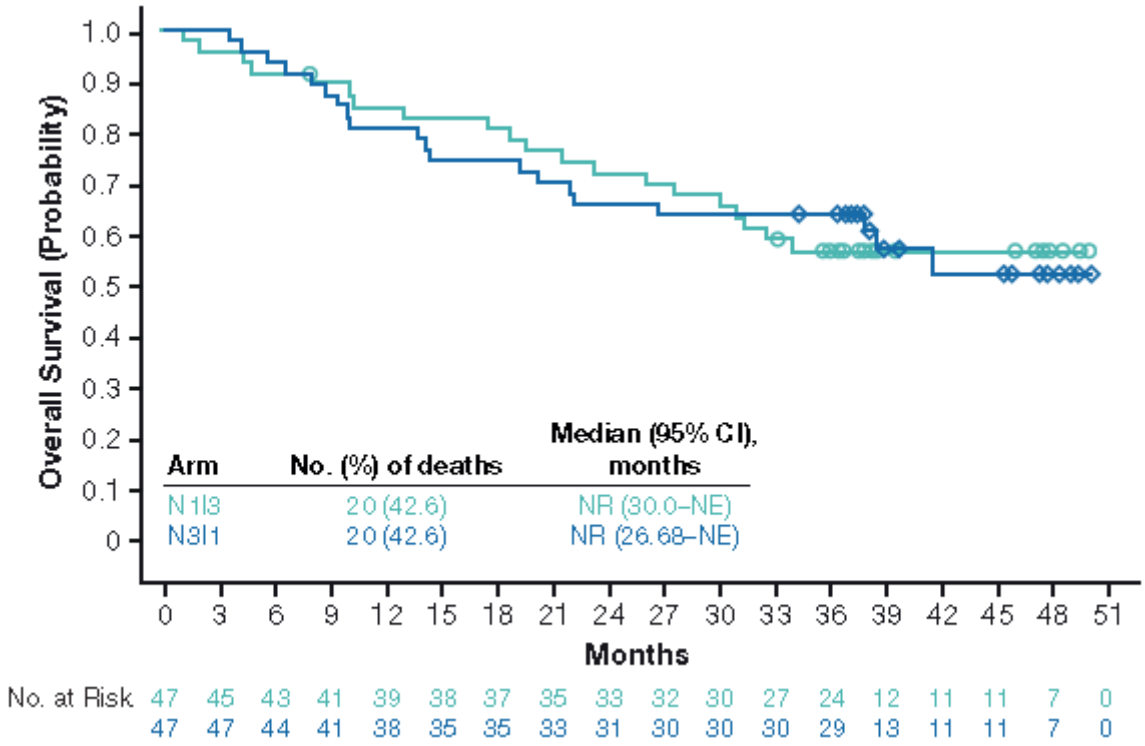
Figure 7: Time to response and duration of response, CheckMate 016, all treated patients



Key: CI, confidence interval; DoR, duration of response; N1I3, nivolumab 1mg/kg + ipilimumab 3mg/kg; N3I1, nivolumab 3mg/kg + Ipilimumab 1mg/kg; NR, not reached.
Source: Plimack *et al.* 2017[34]

Despite the >36-month follow-up, median OS was not reached in either treatment arm, as seen in Figure 8. The 12-month OS rates were 81% in the N3I1 arm and 85% in the N1I3 arm; the respective 24-month OS rates were 66% and 72%.[34]

Figure 8: Overall survival, CheckMate 016, all treated patients

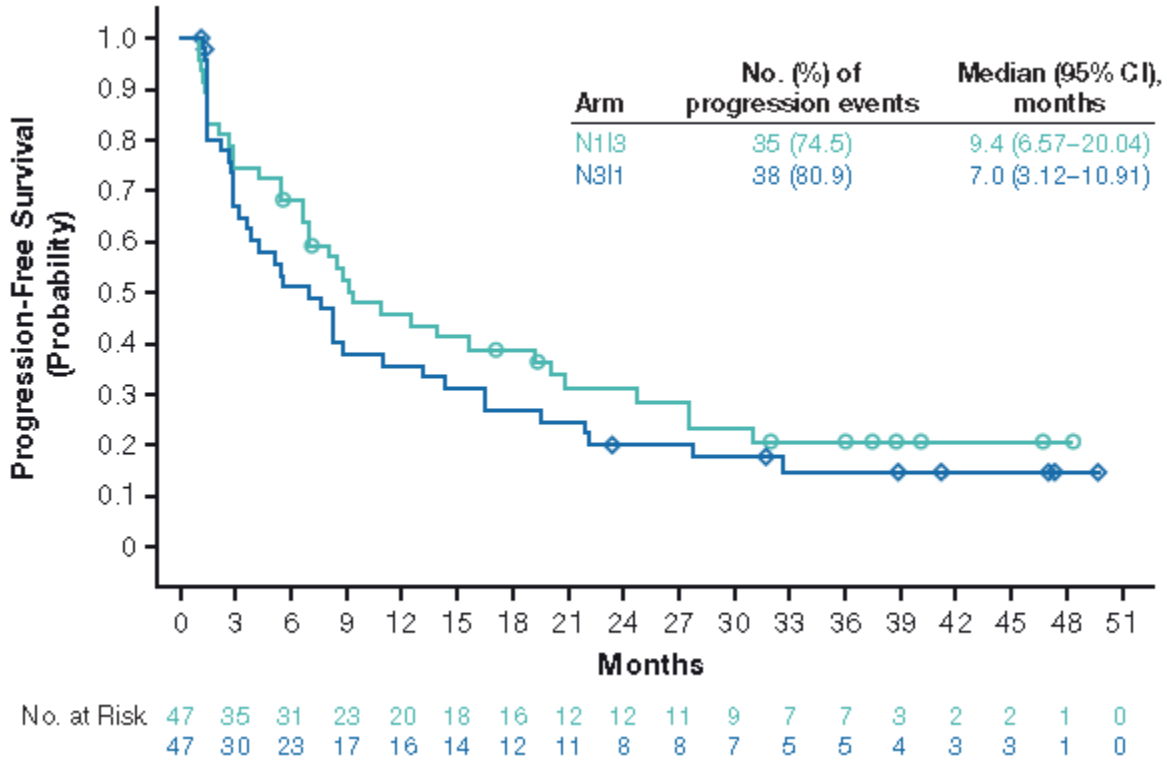


Key: CI, confidence interval; N1I3, nivolumab 1mg/kg + ipilimumab 3mg/kg; N3I1, nivolumab 3mg/kg + ipilimumab 1mg/kg; NE, not evaluable; NR, not reached.
Source: Plimack *et al.* 2017.[34]

A total of 26 (55.3%) patients in the N3I1 arm and 19 (40.4%) patients in the N1I3 arm received subsequent systemic therapy.[34]

Median PFS was 7.0 months in the N3I1 arm and 9.4 months in the N1I3 arm, as presented in Figure 9.[34] The 12-month PFS rates were 36% in the N3I1 arm and 46% in the N1I3 arm; the respective 24-month PFS rates were 20% and 31%.

Figure 9: Progression-free survival, CheckMate 016, all treated patients



Key: CI, confidence interval; N1I3, nivolumab 1mg/kg + ipilimumab 3mg/kg; N3I1, nivolumab 3mg/kg + Ipilimumab 1mg/kg.
Source: Plimack *et al.* 2017.[34]

B.2.7. Subgroup analysis

A summary of subgroup analyses for both intermediate-/poor-risk patients and the total population of CheckMate 214 is presented in Appendix E. Overall, results were consistent with the overall study results.

Exploratory analyses of OS, PFS and ORR were conducted on the favourable-risk population. OS was observed to favour sunitinib (HR: 1.45), although this was not statistically significant with very few events (p=0.2715; 37/249).[33] NIVO+IPI showed improved median PFS (15.3 months) and was 3.7 months longer than that seen with the intermediate- and poor-risk patients.[14] There were even stronger improvements observed in the sunitinib group (25.1 months). The difference in PFS was in favour of sunitinib: HR: 2.18 (99.1% CI: 1.29, 3.68).

Clinical consultation on these findings suggested that the favourable-risk group may show different antigenic signatures in tumours compared to intermediate-/poor-risk patients, with favourable-risk patients having quite 'pure' tumours that are VEGF-driven, whereas tumours from intermediate-/poor-risk patients are more complex with more mutational drivers.[29] As such, intermediate-/poor-risk tumours may develop resistance to VEGFR TKIs more rapidly, and respond better to immune checkpoint inhibitor therapy, than tumours from favourable-risk patients.[29] Furthermore, clinicians felt that in the favourable-risk group, data were still quite immature, with both treatment groups showing positive outcomes, and that with longer follow-up, survival curves may cross. Therefore, NIVO+IPI will outperform sunitinib in the long term, offering a durable long-term survival benefit for a certain proportion of favourable-risk patients, making this immunotherapy combination an effective treatment option for favourable-risk patients as well.

The IRRC-assessed ORR was 28.8% and 51.6% in the NIVO+IPI and sunitinib favourable-risk groups, respectively.[14] However, CR was achieved by 11.2% and 5.6% of patients in the NIVO+IPI and sunitinib groups, respectively. [33] Responses in the NIVO+IPI group were also more durable than in the sunitinib group.

Subgroup results for efficacy by PD-L1 expression, an exploratory endpoint in CheckMate 214, are presented below.

B.2.7.1. Efficacy by PD-L1 tumour expression

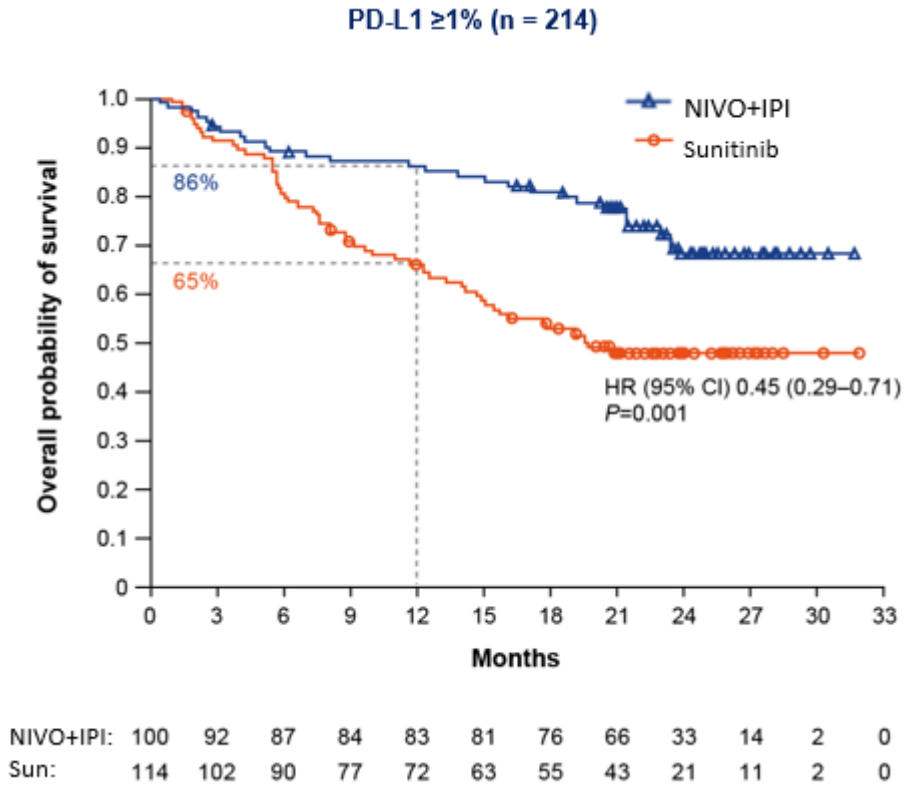
OS

In intermediate-/poor-risk patients, exploratory analyses suggest that OS was favoured in the NIVO+IPI group compared to the sunitinib group, regardless of PD-L1 tumour expression. These data support previous observations that PD-L1 is not a predictive biomarker for nivolumab effect in advanced RCC. This has also been confirmed through consultation with clinicians, who stated that advanced RCC patients would not be treated differently depending on PD-L1 status.[29]

Median OS for ≥1% PD-L1 tumour expression was not reached in the NIVO+IPI group, but was 19.6 months in the sunitinib group (HR: 0.45; 95% CI: 0.29, 0.71), as presented in Figure 10.[36] For patients with <1% PD-L1 tumour expression, median

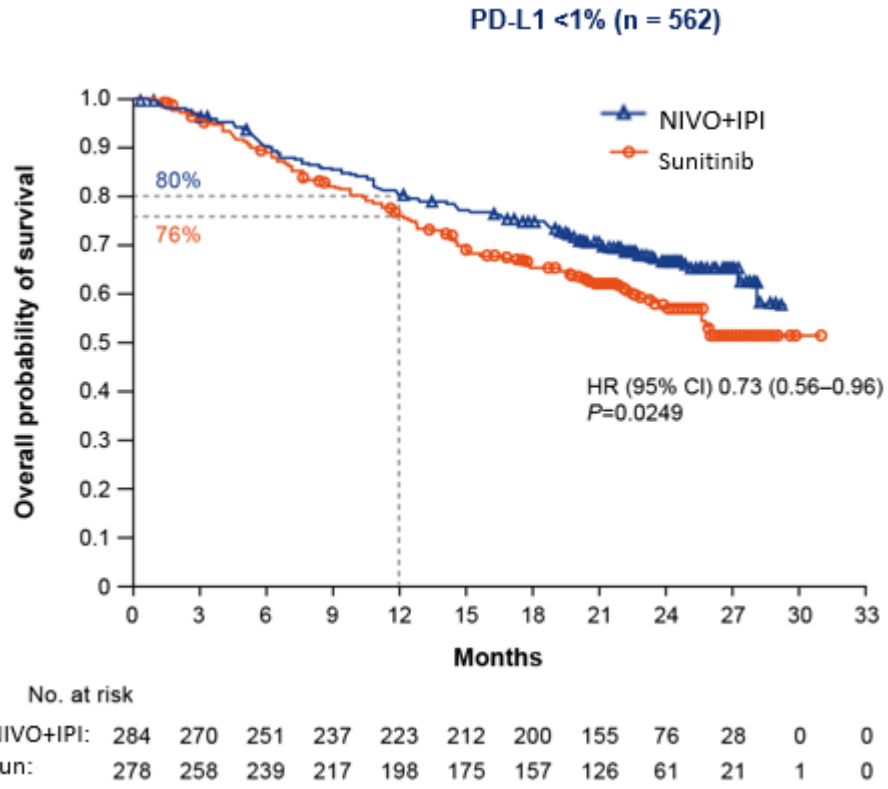
OS was not reached in either treatment group (HR: 0.73; 95% CI: 0.56, 0.96 in favour of NIVO+IPI), as presented in Figure 11.

Figure 10: Kaplan–Meier curve of OS in patients with PD-L1 ≥1%, CheckMate 214, intermediate-/poor-risk patients



Key: CI, confidence interval; HR, hazard ratio; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PD-L1, programmed death receptor ligand-1; Sun, sunitinib.
Source: BMS Data on File[36]

Figure 11: Kaplan–Meier curve of OS in patients with PD-L1 <1%, CheckMate 214, intermediate-/poor-risk patients



Key: CI, confidence interval; HR, hazard ratio; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PD-L1, programmed death receptor ligand-1; Sun, sunitinib.
Source: BMS Data on File[36]

In all randomised patients, including favourable-risk, results of OS by baseline PD-L1 tumour expression [redacted].[33] In an analysis of the predictive relationship of PD-L1 tumour expression for OS, OS was [redacted] in all PD-L1 evaluable subjects with PD-L1 tumour expression ≥1% compared with those with PD-L1 tumour expression < 1% in the NIVO+IPI group (HR: [redacted]). However, in the sunitinib group, OS was [redacted] in subjects with PD-L1 tumour expression <1% compared to those with PD-L1 tumour expression ≥1% (HR: [redacted]), as depicted in Figure 12.

Figure 12: Kaplan–Meier curve of OS based on PD-L1 status, CheckMate 214, all randomised patients

Key: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death receptor ligand-1.
Source: BMS Data on File[36]

PFS

In intermediate-/poor-risk patients, exploratory analyses suggest that the improvements in PFS per IRRC with NIVO+IPI compared to sunitinib were more pronounced in patients with PD-L1 tumour expression ≥1%.[14] Median PFS was significantly longer in NIVO+IPI patients with ≥1% PD-L1 expression (22.8 months) compared to sunitinib patients (5.85 months) (p=0.0003). In patients with <1% expression, median PFS was 11.0 months and 10.4 months in the NIVO+IPI and sunitinib groups, respectively. KM curves for PFS by PD-L1 tumour expression are presented in Appendix E.4.

In all randomised patients, including favourable-risk, PFS was [redacted] in NIVO+IPI patients with ≥1% PD-L1 tumour expression than in sunitinib patients ([redacted] months versus [redacted] months, respectively).[33] In NIVO+IPI patients with <1% PD-L1 tumour expression, PFS was [redacted] than in sunitinib patients ([redacted] months versus [redacted] months, respectively). Of note, poor correlation between PFS and OS in advanced cancer can restrict the relevance of PFS data to patient benefit in the longer-term. [37]

ORR

In intermediate-/poor-risk patients with expression ≥1% PD-L1, an objective response was seen in 58.0% of NIVO+IPI patients compared to 21.9% of sunitinib

patients[14], resulting in an odds ratio (OR) of 4.9 (95% CI: 2.61, 9.34).[33] The results seen in the NIVO+IPI group were also greater in patients with <1% expression, where 37.3% of NIVO+IPI treated patients had an objective response compared to 28.4% of sunitinib patients (OR: 1.5; 95% CI: 1.04, 2.17[33]).[14] In all randomised patients, results of ORR by baseline PD-L1 tumour expression were consistent with those in intermediate-/poor-risk patients.[14]

Time to response was [redacted] for both PD-L1 subgroups when treated with NIVO+IPI compared to sunitinib, and of NIVO+IPI-treated patients was [redacted] in those with PD-L1 expression ≥1% ([redacted] months) compared to patients with expression <1% ([redacted] months). Median duration of response was [redacted] in either NIVO+IPI subgroup, but was [redacted] months and [redacted] months in the sunitinib subgroups of ≥1% and <1% expression, respectively.[33]

B.2.8. Meta-analysis

Meta-analysis has not been performed because a single RCT provides evidence supporting the use of NIVO+IPI for the treatment of previously untreated, advanced RCC in patients with intermediate-/poor-risk disease.

B.2.9. Indirect and mixed treatment comparisons

No studies were identified through the SLR (described in Appendix D) that investigated NIVO+IPI in comparison to pazopanib in patients with intermediate-/poor-risk advanced RCC. Therefore, an indirect treatment comparison (ITC) in the form of a network meta-analysis (NMA) was conducted.

B.2.9.1. Methods

A total of 46 trials were included in the final evidence base identified through the SLR. Of these, 37 trials were included in the NMA; publications were excluded from the analyses due to reporting neither a HR nor a KM curve for PFS and OS. An assessment of clinical heterogeneity was conducted on studies included in the NMA; further details are provided in Appendix D.

The NMA included both a primary analysis conducted in the intermediate-/poor-risk patient group and a secondary analysis conducted in the all-risk patient group. Both analyses used a Bayesian NMA approach, using the HR as primary estimate of

efficacy. The main assumption for this model is the proportional hazards hypothesis, where the treatments' HR between any two treatments is assumed constant in time. The choice of the model was informed by the findings of the individual patient-level data (IPD) analyses from CheckMate 214, where both PFS and OS were found to validate the proportional hazard assumption hypothesis (within the follow-up available).

The NMA focused on PFS and OS with HRs and their associated 95% CIs used as inputs. If a HR was not reported in a publication, but the corresponding KM curve was available, then Guyot's algorithm was carried out to augment the data on which the NMA is based.[38] Guyot's algorithm is an iterative method to reconstruct the IPD from digitised KM curves, along with optional information such as the number-at-risk table and the total number of events for each treatment arm.

The base case of the primary analysis included all identified studies that reported outcomes of interest for first-line treatments available globally in the intermediate-/poor-risk patient group, as per MSKCC criteria (as this was the criteria adopted by all studies reporting risk outside of CheckMate 214). A sensitivity analysis was performed using meta-regression to account for the proportion of patients with favourable MSKCC prognostic factors among studies. Two different scenarios were carried out:

1. When the information (HR) was available among patients with intermediate-/poor-risk MSKCC prognostic factors, the information was used. When unavailable, information on the intention-to-treat (ITT) population was used.
2. Only the information in the ITT population was used for the NMA, even when information was available in intermediate-/poor-risk patients.

When part of a study population was missing, incidences of MSKCC categories were rescaled to add up to 100%. This method was assuming that missing data in MSKCC status were not correlated to a specific category. The secondary analysis was performed on the overall RCC population (irrespective of risk).

Full details of the methodology of the NMA are presented in Appendix D.

B.2.9.2. Results

Key efficacy results of the primary analyses for sunitinib and pazopanib, the comparisons of interest to the NHS, are presented in Table 10. Results of the primary analyses for all first-line treatments available globally (and thus included in the full evidence synthesis), and results of the secondary analyses, are presented in Appendix D.

Overall survival

The base case analysis of OS found that treatment with NIVO+IPI resulted in improved OS compared to sunitinib, with a 100% Bayesian probability of NIVO+IPI being the better treatment (Table 10). Due to a lack of data, the base case analysis did not include comparison to pazopanib. In supportive sensitivity analyses, both scenarios showed a trend towards improved survival after treatment with NIVO+IPI compared with both VEGFR TKI agents (sunitinib and pazopanib).

Progression-free survival

The base case analysis of PFS found that treatment with NIVO+IPI resulted in improved PFS compared to both sunitinib and pazopanib, with a 98% and 97% Bayesian probability of NIVO+IPI being the better treatment, respectively. Across sensitivity analyses, a similar trend was shown, with NIVO+IPI resulting in improved PFS in the majority of cases. The exception to this was the sensitivity analysis Scenario 2, in which no differences were observed in the comparison of NIVO+IPI versus pazopanib.

Table 10: Key efficacy results for primary base case and sensitivity analyses

OS				
Base case results[a]	**Fixed-effect model (DIC=3.196)**		**Random-effect model (non-convergent)**	
	HR [95% CrI]	**P(NIVO+IPI better)**	**HR [95% CrI]**	**P(NIVO+IPI better)**
SUN	0.63 [0.5, 0.8]	100%	0.63 [0.01, 30.85]	79%
PAZ	Data not available for pazopanib in intermediate-/poor-risk patients			
Sensitivity analyses results[b]	**Scenario 1 (DIC=-0.282)**		**Scenario 2 (DIC=-1.738)**	
	HR [95% CrI]	**P(NIVO+IPI better)**	**HR [95% CrI]**	**P(NIVO+IPI better)**
SUN	0.63 [0.5, 0.80]	100%	0.95 [0.4, 2.43]	54%
PAZ	0.42 [0.13, 1.46]	91%	0.67 [0.42, 1.06]	96%
PFS				
Base case results[a]	**Fixed-effects model (DIC=0.73)**		**Random-effects model (DIC=2.21)**	
	HR [95% CrI]	**P(NIVO+IPI better)**	**HR [95% CrI]**	**P(NIVO+IPI better)**
SUN	0.82 [0.68, 0.99]	98%	0.82 [0.01, 58.6]	66%
PAZ	0.78 [0.61, 1.00]	97%	0.78 [0.00, 306.74]	64%
Sensitivity analyses results[b]	**Scenario 1 (DIC=14.316)**		**Scenario 2 (DIC=0.336)**	
	HR [95% CrI]	**P(NIVO+IPI better)**	**HR [95% CrI]**	**P(NIVO+IPI better)**
SUN	0.82 [0.68, 0.99]	98%	0.64 [0.33, 1.23]	91%
PAZ	0.75 [0.58, 0.95]	99%	1.04 [0.74, 1.46]	41%

Key: CrI, credible interval; DIC, deviance information criterion; HR, hazard ratio; NIVO+IPI, nivolumab + ipilimumab; NMA, network meta-analysis; OS, overall survival; P, probability; PAZ, pazopanib; PFS, progression-free survival; SUN, sunitinib.
Notes: [a], Base case analyses used data from intermediate-/poor-risk patients; [b], Scenario 1 used data from intermediate-/poor-risk patients where available and data from all patients with meta-regression for favourable prognosis patients to fill evidence gaps; Scenario 2 used data from all patients with meta-regression for favourable prognosis patients for all studies; fixed-effects model used for sensitivity analyses as random-effects models were non-convergent.

B.2.9.3. Uncertainties and limitations in the indirect treatment comparisons

One of main limitations of the base case analyses was the limited set of available comparators as few studies reported results for the intermediate-/poor-risk group. In addition, for pazopanib, one of the main comparators of interest, information for PFS, was only available in the subgroup of intermediate-risk patients, leading to potential bias for the evaluation of efficacy of nivolumab against it. Furthermore, the subgroup of intermediate-/poor-risk patients was defined using the IMDC scoring system in CheckMate 214, whereas the MSKCC scoring system was used in all other studies, resulting in potential discrepancies in the different risk populations, depending on which tool is used.

A meta-regression sensitivity analysis was carried out with the aim of increasing the available set of comparators. However, the method is associated with both important methodological limitation, with an assumption of similar effect of the covariate for all the treatments and a limited part of the network informing this assumption (given the lack trials assessing the same two treatments); and high uncertainty, leading to none of the treatments being associated with a significant difference when compared with any other. In addition, despite convergence, the results are not aligned with evidence that could be gathered from both IPD (coming from CheckMate 214) and from the published literature (information from the MSKCC intermediate-/poor-risk network, primary analysis). In consequence, results were associated with little value and did not directly allow overcoming the problem of the low set of available comparators.

There are also concerns regarding face validity. The results of the sensitivity analysis indicated a lower performance of NIVO+IPI in the subgroup of intermediate-/poor-risk patients when compared to sunitinib versus the RCC population without restriction for both OS and PFS. This contrasts with the findings from the CheckMate 214 study. This difference is explained by the small number of studies comparing the same set of treatments and with overlapping HRs, leading to a lack of power to truly identify the effect of the covariate from the between-study heterogeneity. It should also be acknowledged that pazopanib has demonstrated statistically non-inferior efficacy to sunitinib in a powered head-to-head trial (COMPARZ), which is arguably a more robust source of evidence on which to base assumptions on indirect efficacy estimates for NIVO+IPI versus pazopanib.[5]

The COMPARZ study was an international, multicentre, Phase III, open-label, parallel-group RCT investigating the comparative efficacy and safety of pazopanib versus sunitinib.[5, 39] The study enrolled treatment-naïve adult patients with clear-cell advanced/metastatic RCC and good performance status (KPS score ≥70) randomised to pazopanib (n=557) or sunitinib (n=553). The primary outcome was PFS assessed by IRRC, and key secondary outcomes included ORR and OS. Non-inferiority between pazopanib and sunitinib was observed across PFS, ORR and OS, as presented in Table 11.

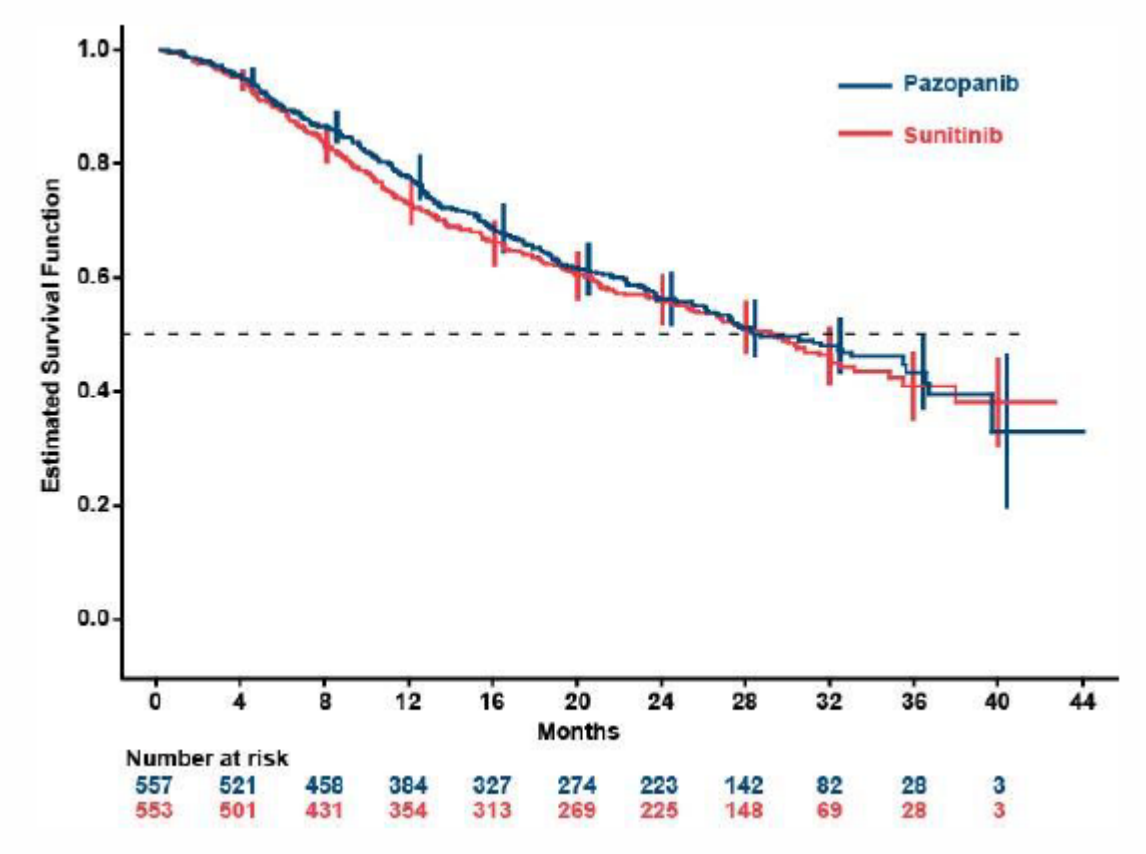
Table 11: Summary of results, COMPARZ study

	Pazopanib (n=557)	**Sunitinib (n=553)**
PFS		
Median months (range)	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)
HR [95% CI]		1.05 [0.90, 1.22]
OS		
Median months (range)	29.3 (26.0, 35.5)	29.1 (25.4, 33.1)
HR [95% CI]		0.92 [0.79, 1.06]
ORR		
N (%)	173 (31)	139 (25)
p-value		0.03

Key: CI, confidence interval; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival
Source: Motzer *et al.* 2013[5]; Motzer *et al.* 2014.[39]

No survival rate data were reported to allow assessment of the probability of long-term survival.[5, 39] However, a KM plot for OS suggests a 2-year OS rate of approximately 55% and a 3-year OS rate of approximately 40% for both treatments (follow-up not reported), as presented in Figure 13.

Figure 13: KM plot of OS from COMPARZ



Key: KM, Kaplan–Meier; OS, overall survival.
Source: Motzer et al. 2013 (supplementary appendix).[5]

B.2.9.4. Conclusion

Reflecting the CheckMate 214 data, based on this Bayesian NMA, NIVO+IPI was shown to be superior to sunitinib, reducing the risk of death by 37% with a 100% probability of being the better treatment. Similarly, with regards to PFS, NIVO+IPI had a 98% probability of being the better treatment, with a HR of 0.82. In the base case analysis for PFS, NIVO+IPI was associated with a reduced risk of death or disease progression of 22% compared to pazopanib, with a 97% probability of being the better treatment. Furthermore, meta-regression results showed that NIVO+IPI was associated with a 33% to 58% reduction in the risk of death compared to pazopanib.

B.2.10. Adverse reactions

B.2.10.1. CheckMate 214

Treatment exposure

A summary of treatment exposure is presented in Table 12.

In this study, 547 patients received at least one infusion of NIVO+IPI and 535 patients received at least one dose of sunitinib. At the time of the final database lock, the median duration of therapy was 7.9 months in the NIVO+IPI group, with a median of [redacted] nivolumab doses and [redacted] ipilimumab doses received, and 7.8 months in the sunitinib group, with a median daily dose of [redacted] mg/day.[33]

Table 12: Treatment exposure in CheckMate 214, all randomised patients

	NIVO+IPI (n=547)		Sunitinib (n=535)
	Nivolumab	**Ipilimumab**	**Sunitinib**
Doses received, mean (SD)	[redacted]	[redacted]	[redacted]
Cumulative dose, mean (SD)	[redacted]	[redacted]	[redacted]
Relative dose intensity, %			
≥110	[redacted]	[redacted]	[redacted]
90 to <110	[redacted]	[redacted]	[redacted]
70 to <90	[redacted]	[redacted]	[redacted]
50 to <70	[redacted]	[redacted]	[redacted]
<50	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Average daily dose, mean mg/day (SD)	[redacted]	[redacted]	[redacted]

Key: N/A, not applicable; NIVO+IPI, nivolumab + ipilimumab; SD, standard deviation.
Source: CheckMate 214 CSR[33]

It is not expected that patients will receive NIVO+IPI treatment for longer than 5 years; indeed, latest data from CheckMate 010, a Phase II study of nivolumab monotherapy in previously treated patients, has shown only [redacted] patients remain on treatment with nivolumab at 5 years.

Subsequent therapy was received by 45.6% and 57.7% of patients in the NIVO+IPI and sunitinib groups, respectively, including 39.5% and 54.0% who received

subsequent systemic cancer therapy, respectively. In the NIVO+IPI arm, 20.2% of patients received subsequent therapy with sunitinib. In the sunitinib group, 28.2% of patients received subsequent therapy with an anti-PD-1 pathway (nivolumab or pembrolizumab).[33] A summary of subsequent therapy is presented in Table 13.

Table 13: Subsequent cancer therapy in CheckMate 214, all randomised patients

	NIVO+IPI (n=550)	Sunitinib (n=546)
Any subsequent therapy, n (%)	251 (45.6)	315 (57.7)
Subsequent radiotherapy, n (%)	63 (11.5)	58 (10.6)
Subsequent surgery, n (%)	30 (5.5)	20 (3.7)
Subsequent systemic therapy, n (%)	217 (39.5)	295 (54.0)
ALK/EGFR tyrosine kinase inhibitors, n (%)	1 (0.2)	0
Erlotinib	1 (0.2)	0
Anti-CTLA-4, n (%)	1 (0.2)	4 (0.7)
Ipilimumab	1 (0.2)	4 (0.7)
Anti-PD-1, n (%)	18 (3.3)	154 (28.2)
Nivolumab	16 (2.9)	147 (26.9)
Pembrolizumab	2 (0.4)	9 (1.6)
Anti-PD-L1, n (%)	0	1 (0.2)
Atezolizumab	0	1 (0.2)
Other immunotherapy, n (%)	9 (1.6)	15 (2.7)
IFN	5 (0.9)	3 (0.5)
IFN-α	0	2 (0.4)
IL-2	0	2 (0.4)
Investigational immunotherapy	4 (0.7)	9 (1.6)
Other systemic cancer therapy – chemotherapy, n (%)	212 (38.5)	227 (41.6)
Other systemic cancer therapy – experimental drugs, n (%)	9 (1.6)	23 (4.2)

Key: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; NIVO+IPI, nivolumab + ipilimumab; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1.
Source: CheckMate 214 CSR[33]

Adverse events

A summary of AEs is presented below; full details are provided in Appendix F.

A summary of adverse events is presented in Table 14.

In intermediate-/poor-risk patients, frequencies of drug-related any-grade serious adverse events (SAEs), drug-related Grade 3–4 SAEs, and AEs leading to discontinuation, were [redacted] in the NIVO+IPI group than in the sunitinib group. Frequencies of drug-related any-grade AEs [redacted] between treatment groups, while the frequency of drug-related Grade 3–4 AEs were [redacted] in the NIVO+IPI group compared to the sunitinib group. Similar patterns were seen for all treated patients.[33]

Table 14: Summary of adverse events in CheckMate 214

	Intermediate-/poor-risk patients		All treated patients	
	NIVO+IPI (n=423)	**Sunitinib (n=416)**	**NIVO+IPI (n=547)**	**Sunitinib (n=535)**
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related	[redacted]	[redacted]	509 (93.1)	521 (97.4)
Grade 3–4 AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related	[redacted]	[redacted]	250 (45.7)	335 (62.6)
Any SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3–4 SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to DC, n (%)	NR	NR	[redacted]	[redacted]
Drug-related	NR	NR	118 (21.6)	63 (11.8)
Deaths due to AE, n (%)	NR	NR	7 (1.3)	4 (0.7)

Key: AE, adverse event; DC, discontinuation; NIVO+IPI, nivolumab + ipilimumab; NR, not reported; SAE, serious adverse event.
Source: Escudier et al. 2017[14]; CheckMate 214 CSR[33]

In intermediate-/poor-risk patients, drug-related AEs were reported in [redacted]% and [redacted]% in the NIVO+IPI and sunitinib groups, respectively.[33] In the NIVO+IPI group, the most frequently reported drug-related AEs were fatigue (33.1%), pruritus (28.8%), diarrhoea (24.1%)[redacted][33].[14] In the sunitinib group, the most frequently reported drug-related AEs were diarrhoea (47.8%), fatigue (44.0%), palmar-plantar erythrodysesthesia syndrome (38.9%) and hypertension (36.3%).[14]

Rates of [redacted] were more commonly seen after treatment with sunitinib compared to NIVO+IPI. In the intermediate-/poor-risk patients, [redacted]% of NIVO+IPI patients reported anaemia ([redacted]% Grade ≥3) compared to [redacted]% of sunitinib-treated patients ([redacted]% Grade ≥3). Similar results were seen in the all treated population: [redacted]% after NIVO+IPI treatment compared to [redacted]% with sunitinib. This pattern was also seen for [redacted] in the all treated population. [redacted] were also seen more commonly in sunitinib-treated patients than NIVO+IPI-treated patients: [redacted]compared to [redacted], respectively. This included diarrhoea, which was reported in [redacted] ([redacted] Grade ≥3) of NIVO+IPI-treated patients and [redacted] ([redacted] Grade ≥3) of sunitinib-treated patients. Pruritus and rash were both reported [redacted] in the NIVO+IPI group ([redacted] and [redacted] respectively) compared to the sunitinib group ([redacted] and [redacted] respectively).[33]

A summary of the most frequent drug-related AEs (reported in ≥15% of patients) is presented in Table 15.

Table 15: Drug-related adverse events reported in ≥15% of patients in CheckMate 214

	Intermediate-/poor-risk patients				All treated patients			
	NIVO+IPI (n=423)		Sunitinib (n=416)		NIVO+IPI (n=547)		Sunitinib (n=535)	
	Any grade	Grade 3-4	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Total patients with an event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	509 (93.1)	250 (45.7)	521 (97.4)	337 (63.0)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	202 (36.9)	23 (4.2)	264 (49.3)	49 (9.2)
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	72 (13.2)	8 (1.5)	91 (17.0)	12 (2.2)
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]	13 (2.4)	0	152 (28.4)	14 (2.6)
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	154 (28.2)	3 (0.5)	49 (9.2)	0
Rash	[redacted]	[redacted]	[redacted]	[redacted]	118 (21.6)	8 91.5)	67 (12.5)	0
PPSE	[redacted]	[redacted]	[redacted]	[redacted]	5 (0.9)	0	231 (43.2)	49 (9.2)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	145 (26.5)	21 (3.8)	278 (52.0)	28 (5.2)
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	109 (19.9)	8 (1.5)	202 (37.8)	6 (1.1)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	59 910.8)	4 (0.7)	110 (20.6)	10 (1.9)
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	23 (4.2)	0	149 (27.9)	14 (2.6)
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	15 (2.7)	0	96 (17.9)	0
Lipase increase	[redacted]	[redacted]	[redacted]	[redacted]	90 (16.5)	56 (10.2)	58 (10.8)	35 (6.5)
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	85 (15.5)	2 (0.4)	134 (25.0)	1 (0.2)
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	75 (13.7)	7 (1.3)	133 (24.9)	5 (0.9)
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	31 (5.7)	0	179 (33.5)	1 (0.2)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	34 (6.2)	2 (0.4)	83 (15.5)	24 (4.5)
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	2 (0.4)	0	95 (17.8)	25 (4.7)
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	12 (2.2)	4 (0.7)	216 (40.4)	85 (15.9)

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIVO+IPI, nivolumab + ipilimumab; NR, not reported; PPES, Palmar-plantar erythrodysesthesia syndrome.
Source: Escudier *et al.* 2017[14]; CheckMate 214 CSR[33]

Select AEs of special clinical interest that are potentially associated with the use of nivolumab are presented in Appendix F. Additional analyses of immune-mediated adverse events (IMAEs) were conducted in order to further characterise AEs of special clinical interest. IMAEs are specific events that include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine disorders (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus).

The most frequently reported any-grade IMAE categories with NIVO+IPI treatment were [redacted]. The majority of IMAEs were [redacted], with the exception of [redacted]. Across IMAE categories, [redacted].[33]

A summary of IMAEs in the all randomised population is presented in Table 16.

Table 16: Immune-mediated adverse events in CheckMate 214, all treated patients

	All treated patients			
	NIVO+IPI (n=547)		Sunitinib (n=535)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
N (%):				
Rash	93 (17)	16 (3)	[redacted]	[redacted]
Diarrhoea/colitis	55 (10)	27 (5)	[redacted]	[redacted]
Hepatitis	38 (7)	33 (6)	[redacted]	[redacted]
Nephritis and renal dysfunction	27 (5)	11 (2)	[redacted]	[redacted]
Pneumonitis	22 (4)	11 (2)	[redacted]	[redacted]
Hypersensitivity/infusion reaction	5 (1)	0 (0)	[redacted]	[redacted]
Hypothyroidism	104 (19)	3 (0.5)	[redacted]	[redacted]
Hyperthyroidism	66 (12)	4 (0.7)	[redacted]	[redacted]
Adrenal insufficiency	44 (8)	16 (3)	[redacted]	[redacted]
Hypophysitis	27 (5)	16 (3)	[redacted]	[redacted]
Thyroiditis	16 (3)	1 (0.2)	[redacted]	[redacted]
Diabetes mellitus	16 (3)	5 (1)	[redacted]	[redacted]

Key: NIVO+IPI, nivolumab + ipilimumab.
Source: Escudier *et al.* 2017[14]; CheckMate 214 CSR[33]

Hypersensitivity/infusion reactions (all-causality, any-grade) were reported in [redacted] patients in the NIVO+IPI group compared to [redacted] patients in the sunitinib group. Of patients in the NIVO+IPI arm, [redacted] were considered to be drug-related, although all w[redacted]. Overall, [redacted] patients had resolution of their events with a median time to resolution of [redacted].[33]

B.2.10.2. CheckMate 016

A summary of TRAEs that occurred in ≥20% of patients is presented in Table 17.

Compared to the N1I3 dose, fewer patients treated at the N3I1 dose experienced Grade 3/4 TRAEs.[34] The most common Grade 3/4 TRAEs with possible immune-mediated aetiology in the N3I1 and N1I3 arms, respectively, were gastrointestinal (4.3% and 23.4%) and hepatic (6.4% and 21.3%). Other Grade 3/4 select TRAEs reported in the N3I1 and N1I3 arms, respectively, were renal (4.3% and 4.3%),

endocrinopathy (4.3% and 0.0%), and skin (0.0% and 2.1%). There were no treated-related deaths in either study arm.

Table 17: TRAEs in ≥20% of patients, all treated patients

	N3I1 (n=47)		N1I3 (n=47)	
	Al grades	**Grade 3/4**	**All grades**	**Grade 3/4**
Any TRAE, n (%)	43 (91.5)	18 (38.3)	45 (95.7)	29 (61.7)
Fatigue	26 (55.3)	0	32 (68.1)	3 (6.4)
Rash	14 (29.8)	0	12 (25.5)	0
Pruritus	15 (31.9)	0	17 (36.2)	0
Nausea	13 (27.7)	1 (2.1)	21 (44.7)	0
Arthralgia	11 (23.7)	0	10 (21.3)	0
Diarrhoea	11 (23.4)	2 (4.3)	22 (46.8)	7 (14.9)
Chills	11 (23.4)	0	4 (8.5)	0
Pyrexia	11 (23.4)	2 (4.3)	7 (14.9)	0
Hypothyroidism	9 (19.1)	0	13 (27.7)	0
Increased lipase	9 (19.1)	7 (14.9)	15 (31.9)	12 (25.5)
Increased AST	8 (17.0)	2 (4.3)	16 (34.0)	6 (12.8)
Increased ALT	7 (14.9)	2 (4.3)	14 (29.8)	10 (21.3)
Decreased appetite	6 (12.8)	0	14 (29.8)	0
Vomiting	7 (14.9)	1 (2.1)	11 (23.4)	0

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N1I3, nivolumab 1mg/kg + ipilimumab 3mg/kg; N3I1, nivolumab 3mg/kg + ipilimumab 1mg/kg; TRAE, treatment-related adverse event.
Source: Plimack *et al.* 2017.[34]

With the N3I1 arm demonstrating a more favourable safety profile and comparable efficacy compared to the N1I3 arm, these results supported the investigation of the N3I1 schedule in the subsequent CheckMate 214 study.

B.2.10.3. Safety overview

The overall safety profile of NIVO+IPI was acceptable compared to sunitinib, and no new safety concerns were identified. In patients with intermediate-/poor-risk, Grade ≥3 all-causality and Grade ≥3 drug-related AEs were both less frequent with NIVO+IPI than with sunitinib. Although a higher proportion of patients discontinued NIVO+IPI due to toxicity, the mean number of ipilimumab doses received in the total population was 3.6 (of a total of 4), showing that overall this treatment was well-tolerated. Most IMAEs were Grade 1–2, the majority of which resolved and were

manageable using the recommended treatment guidelines for early work-up and intervention.

The safety profiles of nivolumab and ipilimumab are already well-established as monotherapies in their respective indications and as combination therapy in advanced melanoma. It should be noted that the established combination in advanced melanoma is at a different dosing schedule to that proposed for this indication; in melanoma, the dose of nivolumab is 1mg/kg and the dose of ipilimumab is 3mg/kg. Both regimens were investigated in the CheckMate 016 study, and the selected N3I1 regimen taken forward to the CheckMate 214 study was in acknowledgement of the more favourable toxicity profile (see Section B.2.10.2).

Although some additive toxicity can be expected during the concomitant phase of combination therapy, events reported in CheckMate 214 are consistent with the established safety profiles of immunotherapy, typically consisting of IMAEs. In second-line advanced RCC, a low rate of Grade 3/4 TRAEs (19%) and discontinuations due to TRAEs (8%) were identified with the use of nivolumab monotherapy (CheckMate 025).[40] Importantly, no deaths related to study-drug toxicity were reported across trials of nivolumab in advanced RCC, further supporting its tolerability profile. Due to the use of nivolumab in second-line RCC, clinicians are familiar with the monitoring and management of common side effects. As experience and familiarity with combination treatment grows, quick and effective management of common side effects is likely to continually improve.

As such, NIVO+IPI demonstrates a favourable benefit–risk profile for the treatment of intermediate-/poor-risk patients with untreated, advanced RCC with well-established and clinically manageable safety data of an alternative profile to currently used sunitinib.

B.2.11. Ongoing studies

Both the CheckMate 214 and CheckMate 016 studies detailed above are ongoing.

Other ongoing studies include the Phase IV, non-randomised CheckMate 920 study of NIVO+IPI in patients with previously untreated advanced or metastatic RCC; the primary completion date for this study is estimated to be March 2018.[41] In addition,

CheckMate 800 is a Phase II, randomised study of multiple administration regimens for NIVO+IPI in patients with RCC; this study is ongoing until 2021.[42] Finally, a randomised Phase II trial of nivolumab in combination with alternatively scheduled ipilimumab in the first-line treatment RCC (Study CA209-814) is ongoing.

B.2.12. Innovation

NIVO+IPI is the first immunotherapeutic agent licensed for use in first-line metastatic RCC and thus represents a 'step-change' in the management of this disease for patients. Indeed, NIVO+IPI was awarded with a Promising Innovative Medicine (PIM) designation in September 2017, reflective of the innovative nature of this treatment, and EAU guidelines now recommend NIVO+IPI as standard of care treatment in intermediate-poor-risk patients. This combination builds upon the value of nivolumab in the second-line RCC setting, which was the first targeted immunotherapy in advanced RCC to demonstrate proven survival benefit, significant clinical response and improved HRQL. As the RCC landscape expands, treatment sequencing will become ever more important; with the introduction of NIVO+IPI in the first-line setting, patients will gain unprecedented advantages as they are able to achieve an immunotherapeutic effect earlier in their treatment pathway.

Standard UK management in the first-line setting is currently restricted to systemic agents of one class (VEGFR TKIs) that have no proven significant benefit on OS and can be associated with significant toxicity. NIVO+IPI offers patients an alternative treatment modality, which has demonstrated an unprecedented survival benefit in the treatment-naïve setting compared with current standard of care (HR: 0.63[14]) in intermediate-/poor-risk patients. Furthermore, the immunotherapeutic effect of NIVO+IPI offers an alternative safety profile to sunitinib that is manageable and familiar to clinicians already accustomed to using nivolumab treatment in the second-line setting.

While we would anticipate the health-related benefits, such as improved survival and response benefits, to be captured in the quality-adjusted life year (QALY) calculation, their significance to patients along with the fact that NIVO+IPI provides the first checkpoint inhibitor immunotherapy option for first-line advanced RCC should be viewed as innovative. Indeed, the introduction of NIVO+IPI would change the

treatment paradigm for such patients and thus represents a ‘step-change’ in the management of this condition.

B.2.13. Interpretation of clinical effectiveness and safety evidence

Standard first-line management in the NHS is currently restricted to systemic VEGFR TKI agents that have no proven significant benefit on OS, and can be associated with significant toxicity.[28, 30, 31, 43] There is a clear unmet need for new treatment modalities to improve physician and patient choice and potentially improve the life expectancy of patients.

In intermediate-/poor-risk patients (a population with the highest unmet medical need and most severe prognosis), NIVO+IPI demonstrated an unprecedented survival benefit, with a superior OS compared to the current standard of care, sunitinib, reducing the risk of death by 37% in CheckMate 214. The separation of the OS curves was observed early in the study, yielding a statistically significant and clinically meaningful OS benefit at the first planned interim OS analysis, and leading the data monitoring committee (DMC) to recommend early termination of the study. Coupled with supportive data from CheckMate 016, NIVO+IPI has clearly shown the potential to significantly improve the life expectancy of patients with previously untreated advanced RCC and to offer the probability of long-term survival to a proportion of patients.

In addition to the survival benefit seen with NIVO+IPI, intermediate-/poor-risk patients also demonstrated significantly higher IRRC-assessed ORR, compared to sunitinib. Responses were deeper, including 9.4% of patients achieving CR, and more durable, with a median DoR not reached and 72% of responding patients with an ongoing response at the time of this analysis (after a median follow-up of 25.2 months). Subsequent analysis of the 214 data has suggested that 30% of patients with a response in the CheckMate 214 study are durable responders; this is further discussed in Sections B.2.6.1 and B.3.3.2. This is particularly meaningful as those patients with a durable response to first-line immune checkpoint inhibitor therapy have the potential for an improved quality of life and survival benefit without the need for further toxic systematic treatment. Indeed, the new modality of NIVO+IPI results

in a manageable safety profile, distinct from currently used systemic VEGFR TKI therapies, and familiar to treating clinicians.

The potential for long-term survival with NIVO+IPI is further supported across the wider clinical evidence base and is based on sound biological rationale encompassing the nature of RCC as an immunogenic tumour and, thus, conducive to immunotherapy treatment. A survival plateau representing an immunotherapy-survival tail was first observed in patients with advanced melanoma who were treated with ipilimumab monotherapy. A pooled analysis of 1,861 patients showed a survival curve that began to plateau at 3 years and extended through to at least 10 years.[44] Such a survival plateau has since been suggested in RCC, and OS rates up to 5 years for previous studies of nivolumab monotherapy in RCC are presented in Table 18. In previously-treated advanced RCC patients, notable 5-year OS rates of 34% (CheckMate 003) and [redacted] (CheckMate 010) are observed. In the larger CheckMate 010 trial (n=167), the proportion of patients surviving for at least 5 years closely reflects the proportion of patients achieving a durable response to treatment (22%[45]), supporting clinical expert opinion that patients with a durable response to immunotherapy can experience long-term survival.[46]

Long-term survival is not a feature of currently available therapies, as further discussed within end-of-life considerations. In a recent retrospective analysis of data in 5,714 patients with metastatic RCC treated with sunitinib in 8 Phase II or III clinical trials (n=1,173) or a global expanded access programme (n=4,543), 84.3% of patients did not achieve a long-term response (defined as having PFS ≥18 months).[47]

Table 18: OS in CheckMate 003, CheckMate 010 and CheckMate 025

Study	Phase	Outcome	Value	Reference
CheckMate 003	Ib	2-year OS	48%	McDermott et al. 2015[48]
CheckMate 010	II		48 % (42–52% depending on dose)	Plimack et al. 2015[49]
CheckMate 025	III		52%	Sharma et al. 2017[50]
CheckMate 003	Ib	3-year OS	44%	McDermott et al. 2015[48]

Study	Phase	Outcome	Value	Reference
CheckMate 010	II		35% (33–40% depending on dose)	Plimack et al. 2015[49]
CheckMate 025	III		39%	Sharma et al. 2017[50]
CheckMate 003	Ib	4-year OS	38%	McDermott et al. 2015[48]
CheckMate 010	II		29%	McDermott et al. 2016[45]
CheckMate 003	Ib	5-year OS	34%	McDermott et al. 2016[45]
CheckMate 010	II	5-year OS	[redacted]	Data on file
Key: OS, overall survival.				

The dual-checkpoint blockade seen with NIVO+IPI combination therapy has shown enhanced anti-tumour responses in pre-clinical studies, compared to single-checkpoint blockade.[51] This has also been observed in the Phase III RCT of NIVO+IPI in advanced melanoma, CheckMate 067. The same synergistic effect can be expected with the use of NIVO+IPI in previously untreated, advanced RCC. This combination thus offers additional potential for improved life expectancy and the probability of long-term survival compared to the recently adopted nivolumab monotherapy. Moreover, introducing immune checkpoint inhibitor therapy earlier in the treatment pathway, when patients have a better preserved immune system and better prognosis, should result in an even greater clinical benefit.[52]

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 NIVO+IPI for the treatment of intermediate-/poor-risk patients with previously untreated, advanced RCC.

Both CheckMate 214 and the supportive Phase I study CheckMate 016 were 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 pivotal CheckMate 214 study was primarily designed to assess OS, PFS and ORR, outcomes of direct relevance to clinical practice. Of particular note, life expectancy (demonstrated by improved OS) is of primary interest to patients with advanced RCC, particularly those with a poor prognosis. None of the current first-line treatment options for patients with advanced RCC have demonstrated an OS benefit in a Phase III setting[28, 43], and real-world analyses show no long-term survival benefit[53] (see end-of-life considerations). With regard to response, when assessing immunotherapies in clinical practice, this will be largely 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. Patients were permitted to receive treatment beyond RECIST-defined progression in CheckMate 214 as a reflection of this practice. However, it is important to note that progression assessments of immunotherapies against RECIST criteria for tumour progression in clinical trials therefore provide a conservative estimate of benefit from therapy compared to clinical practice assessment of immunotherapy treatment effect; this should be considered when interpreting PFS data.

The CheckMate 214 study is generally reflective of patients presenting for first-line treatment of advanced RCC in UK clinical practice. Although patients enrolled in CheckMate 214 were of slightly younger age compared to mean demographics of patients with untreated advanced RCC, trial results are anticipated to be reflective of the advanced RCC population. European sites represented 40% of all involved, including four in England. Furthermore, clinical experts practising in the field of RCC confirmed that they would be comfortable applying CheckMate 214 trial results to patients presenting in UK clinical practice.[54]

Importantly, CheckMate 214 directly compared NIVO+IPI with sunitinib, one of the comparators named in the decision problem and representative of the current standard of care treatment strategy of monotherapy VEGFR TKI at first-line. Although head-to-head data are not available for comparison to pazopanib, equivalence between sunitinib and pazopanib is well-accepted on the basis of non-inferiority demonstrated in the COMPARZ trial (see Section B.2.9), as confirmed through clinical validation.[54] Furthermore, an NMA has been conducted that demonstrates this, as well as showing a superior OS and PFS benefit with NIVO+IPI compared to pazopanib.

In conclusion, NIVO+IPI combination therapy offers an innovative immunotherapy combination with the potential to significantly improve the life expectancy of intermediate-/poor-risk patients with previously untreated, advanced RCC, and offer the probability of long-term survival to a proportion of these patients.

End-of-life treatment considerations

Patients with advanced RCC have a life-threatening condition and face a worsening life expectancy with increasing adverse prognostic factors. When diagnosed with intermediate-/poor-risk disease, patients can arguably be considered as facing end-of-life in current practice. A pool of clinical evidence (Phase III RCT data and real-world evidence) indicates that around half of them are unlikely to survive for more than 2 years when treated with standard-of-care VEGFR TKI agents in the first-line setting and life expectancy can be as low as 6 months for poor-risk patients (Table 19). Expert opinion is that the life expectancy of patients with intermediate-/poor-risk advanced RCC in real-world practice does not regularly exceed 24 months.

Although the CheckMate 214 study has immature follow-up and thus cannot confirm the magnitude of survival benefit for NIVO+IPI versus current standard-of-care, the economic model based on CheckMate 214 data has shown a survival gain in the order of years, rather than months, far exceeding the standard additional survival criterion for end-of-life treatments.

These considerations are summarised in Table 19.

Table 19: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	Phase III trial data investigating sunitinib in the first-line IMDC intermediate-/poor-risk advanced RCC setting (n=422): median OS = 26.0 months; estimated 2-year OS (based on KM data) = 53%[33]	Section B.2.6.1 Page 29
	Phase III trial data investigating sunitinib or pazopanib in the first-line advanced RCC setting irrespective of risk (n=1,775): median OS = 22.9 to 29.1 months; estimated 2-year OS = 55% (based on KM data of pivotal trials)[27, 28, 39]	Section B.2.9 Page 43

	International, population-based study investigating survival differences in the IMDC intermediate-/poor-risk metastatic RCC setting following first-line VEGF-targeted therapy (n=849): median OS = 22.5 months for intermediate-risk patients, 7.8 months for poor-risk patients[13]	Section B.1.3 Page 11
	Population-based study (Czech Republic) investigating survival differences in the IMDC intermediate-/poor-risk metastatic RCC setting following first-line sunitinib therapy (n=495): median OS = 24.8 months for intermediate-risk patients, 9.3 months for poor-risk patients[55]	Not previously referenced
	Population-based study (Netherlands) investigating sunitinib in the first-line metastatic RCC setting (n=391): median OS = 9-10 months for all patients; median OS = 6-7 months for poor-risk patients[56]	Not previously referenced
	Global expanded access programme of sunitinib in the first-line advanced RCC setting irrespective of risk (n=4,543): median OS = 19.0 months[53]	Not previously referenced
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.	Estimated improvement in 2-year OS rate with NIVO+IPI (vs sunitinib) = 12% (65% vs 53%) based on KM data from CheckMate 214[33]	Section B.2.6.1 Page 29
	Estimated improvement in 3-year OS rate with NIVO+IPI (vs sunitinib) = 16% (54% vs 38%) based on economic modelling. Estimated additional years of life with NIVO+IPI (vs sunitinib) = 3.94 based on economic modelling.	Section B.3.7, Page 147.
Key: IMDC, International Metastatic RCC Database Consortium; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search for economic evaluations of NIVO+IPI for previously untreated patients with advanced and/or metastatic RCC, documented in Appendix G, identified no such studies.

However, the history of NICE appraisals for newly available treatments for previously untreated, advanced RCC highlights the methods and data used for economic evaluation. Recommendations for sunitinib (NICE Technology Appraisal [TA] 169), pazopanib (NICE TA215) and most recently tivozanib (NICE ID591) have been based on similar approaches to estimate cost effectiveness. In each of these, a partitioned survival model has been used to directly capture the key clinical outcomes of PFS and OS.

B.3.2. Economic analysis

B.3.2.1. Patient population

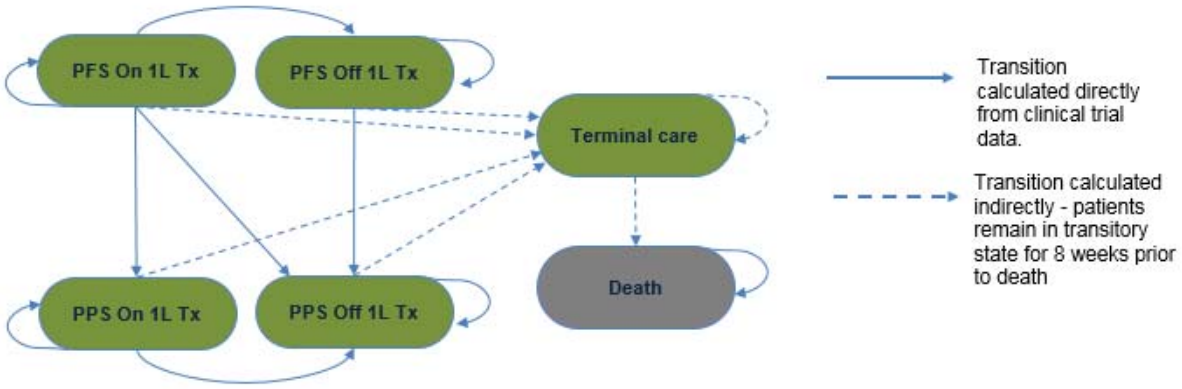
As described in Section B.1.2, the anticipated marketing authorisation for NIVO+IPI is to treat previously untreated, advanced RCC in adults with intermediate- or poor-risk. Though favourable-risk patients were included in the CheckMate 214 ITT population, the co-primary endpoints of CheckMate 214 were tested in intermediate- and poor-risk patients only, and in line with the NICE Final Scope, the economic analysis focuses on clinical outcomes for these patients.

B.3.2.2. Model structure

In line with the approaches in TA169, TA215 and TA591, a cohort-level partitioned survival modelling approach is used. This modelling approach is also consistent with the economic analysis informing the 2016 appraisal of nivolumab monotherapy for previously treated, advanced RCC (TA417), the only previous STA of an immune checkpoint inhibitor treatment strategy in renal cancer.

Figure 14 illustrates the health states and possible transitions in each model treatment arm. The health states capture treatment status as well as disease progression, and are consistent with the care pathway and treatment-dependent costs and health outcomes associated with each component, as is illustrated throughout Sections B.3.3, B.3.4 and B.3.5. The PFS and post-progression survival (PPS) "Off 1L Tx" health states are notable as a QALY adjustment is applied to the proportion of the cohort entering each of these states; this is to account for the expected patient utility implications of anticipated second-line treatment, as described in Section B.3.4.4.

Figure 14: Economic model health states and structure, one treatment arm



Key: 1L Tx, first-line treatment for advanced renal cell carcinoma; PFS, progression-free survival; PPS, post-progression survival.

Table 20 summarises and justifies some key features of the economic analysis, in comparison to the corresponding features of TA169, TA215, ID591 and TA417, illustrating how the approach has been designed for consistency with (i) previous relevant TAs, (ii) the *Guide to the Methods* Reference Case[57], and (iii) methodological guidance from the Institute.

A 1-week cycle length is considered sufficiently short to accurately capture key clinical outcomes and dosing regimens. Given the short cycle length, a half-cycle correction is not applied to any cost or health outcomes.

Table 20: Features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	TA169	TA215	ID591	TA417	Chosen values	Justification
Appraisal	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma	Pazopanib for the first-line treatment of advanced renal cell carcinoma	Tivozanib for treating renal cell carcinoma	Nivolumab for previously treated advanced renal cell carcinoma		
Time horizon	10 years Not justified	10 years Depending on effectiveness assumptions, 99% of all patients estimated to be dead within 10 years[26]	10 years Based on the company's estimation that most patients would have died by this time point[58]	30 years >99% of patients on any model arm estimated to be dead within 30 years[59]	40 years	>99% of patients on any model arm estimated to be dead within 40 years Consistency with the NICE Reference case
Extrapolation of treatment effectiveness	Parametric survival modelling of bevacizumab plus IFN versus IFN RCT, with HR for sunitinib applied from sunitinib versus IFN RCT.[60] Extrapolation of treatment effectiveness implied by this approach.	The pivotal placebo-controlled RCT, VEG105192, allowed placebo patients to switch to pazopanib upon progression.[26] Treatment effectiveness estimation versus placebo relied on adjustment for	The pivotal RCT, TIVO-1, tested tivozanib versus sorafenib and allowed sorafenib patients to switch to tivozanib upon progression.[61] The need for indirect treatment	Parametric survival model fits to pivotal RCT CheckMate 025 data for company and ERG base case, with a scenario for a curative immune checkpoint inhibitor effect for some long-term survivors, based on advice from two oncologists,[59] with	Parametric survival model fits to CheckMate 214 data, with a curative immune checkpoint inhibitor survival effect for some long-term survivors.	Consistency with (i) NICE Reference Case and DSU TSD 14 guidance, (ii) previous appraisals in treatment-naïve, advanced RCC, and (iii) the only previous TA of an immune checkpoint inhibitor for

Factor	Previous appraisals				Current appraisal	
	TA169	TA215	ID591	TA417	Chosen values	Justification
		cross-over bias, and versus relevant comparators relied further on indirect comparisons. Extrapolation of treatment effectiveness based on parametric survival modelling.	comparisons to link outcomes to relevant comparators and to attempt to adjust for cross-over bias meant understanding 'within-trial' treatment effectiveness was challenging.	assumptions of effectiveness equivalence for TKIs axitinib and everolimus imposed by the ERG and accepted by the committee. "The committee preferred the methods in the company's base case…but it was willing to consider scenarios with predictions of better survival in its decision-making."[62]		advanced RCC, (completed in 2016). See Section B.3.3 for further explanation and justification.
Source of utilities	Estimates from patient-reported EQ-5D-3L data from Phase II and III sunitinib trials[43, 63]; UK valuation tariff[60]	PFS: Patient-reported EQ-5D-3L data from VEG105192; UK valuation tariff[26] PPS: Published literature[26]	Patient-reported EQ-5D-3L data from TIVO-1; valuation tariff not reported[58]	Statistical analysis of EQ-5D-3L data from CheckMate 025; UK valuation tariff. Previous TA estimates for relevant comparators outside of CheckMate 025.[59]	First-line and underlying long-term utility: statistical analysis of EQ-5D-3L data from CheckMate 214; UK valuation tariff. Second-line utility: statistical analysis of EQ-5D-3L data from	Consistency with (i) NICE Reference Case, (ii) previous appraisals in treatment-naïve, advanced RCC, and (iii) the only previous TA of an immune checkpoint

Factor	Previous appraisals				Current appraisal	
	TA169	TA215	ID591	TA417	Chosen values	Justification
					CheckMate 025, UK valuation tariff	inhibitor for advanced RCC. See Section B.3.4 for further explanation and justification.
Source of costs	Relative dose intensities incorporated into the base case cost-effectiveness analysis[60] "Assumptions… based on guidelines outlining current practice and the information provided by clinicians in the expert advisory group."[60]	Relative dose intensities considered[26] Monthly blood tests, consultant-led outpatient visits and 3-monthly CT scans pre-progression. GP, community nurse and pain medication post-progression. Assumptions based on TA169.[26]	Relative dose intensities considered by ERG, in line with previous TAs[58] Monthly outpatient consultant meeting, blood count and liver count. Three-monthly CT scan and thyroid function test. In line with ERG expert advice and previous TAs.[61]	Relative dose intensities considered.[62] Four-weekly GP visit and blood test. Twelve-weekly CT-scan PFS only. Speciality community nurse visit 3 times over every 8 weeks and daily pain medication PPS only. In line with most recent previously treated RCC TA (TA333), and expert advice.[59]	Relative dose intensities considered.[62] Resource use assumptions from TA417, validated for intermediate-/poor-risk previously untreated advanced RCC patient group by clinical experts.	Consistency with (i) NICE Reference Case, (ii) the only previous TA of an immune checkpoint inhibitor for advanced RCC (completed in 2016) and (iii) expert clinician advice. See Section B.3.5 for further explanation and justification.

Key: DSU, Decision Support Unit; EQ-5D-3L, EQ-5D 3-level questionnaire; ERG, Evidence Review Group; HR, hazard ratio; IFN, interferon; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; RCC, renal cell carcinoma; RCT, randomised controlled trial; TA, Technology Appraisal; TKI, tyrosine kinase inhibitor; TSD, Technical Support Document.

B.3.2.3. Intervention technology and comparators

In line with the final scope, the comparators for NIVO+IPI in adults with advanced RCC with poor- or intermediate-risk are sunitinib and pazopanib.

NIVO+IPI, sunitinib and pazopanib are each implemented in the model as per anticipated (NIVO+IPI) or agreed (sunitinib[64], pazopanib[65]) EMA marketing authorisations, and in-line with the pivotal RCTs supporting their use in previously untreated, advanced RCC patients.[28, 33, 43, 66]

As described in Section B.1.2, nivolumab is administered by intravenous (IV) infusion at an initial dose of 3mg/kg alongside an IV dose of 1mg/kg ipilimumab, every 3 weeks for four treatment cycles. From Treatment Cycle 5 onwards, nivolumab is administered every 2 weeks at a dose of 3mg/kg.

In May 2017, Bristol-Myers Squibb (BMS) submitted posology variation proposals for a fixed dose of nivolumab at (i) 240mg q2w or (ii) 480mg q4w, as feasible and practical alternatives to CheckMate 214 nivolumab dosing. As either posology may be relevant to the final license, each is considered in a scenario in Section B.3.8.3. The economics of alternative dosing regimens, described as a “hybrid” approaches, are also considered as scenarios in Section B.3.8.3. In two scenarios, NIVO+IPI patients are assumed to receive CheckMate 214 nivolumab dosing for the first 12 weeks (four 3-week dosing cycles), followed by either 240mg nivolumab q2w or 480mg nivolumab q4w.

Sunitinib and pazopanib are each administered orally. Sunitinib patients receive a recommended dose of 50mg once daily for the first 4 weeks of 6-week treatment cycles.[64] Pazopanib is administered orally at a recommended doses of 800mg once daily.[65, 67, 68]

In CheckMate 214, patients could withdraw from study participation due to unacceptable toxicity or disease progression. In line with the known mechanism of action of the intervention, patients could also receive treatment beyond RECIST-defined disease progression, in both arms of the study, based on investigator assessment of ongoing clinical benefit. In the pivotal Phase III RCTs for each VEGFR TKI comparator, doses could be reduced to manage toxicity, and treatment

discontinuation was specified for unacceptable toxicity, withdrawal of consent, disease progression or death.[28, 43] Time to treatment discontinuation (TTD) data from CheckMate 214 are used to accurately capture treatment duration assumptions for NIVO+IPI and sunitinib in the economic model, as described in Section B.3.3, while publicly available data from previous TAs and the published literature are used to help inform treatment duration assumptions for pazopanib, as described in Section B.3.5.1. BMS believe that in RCC the maximum treatment duration would be less than 5 years from NIVO+IPI treatment initiation. This assumption is incorporated into the economic analysis base case, as described in Sections B.3.3.4 and B.3.5.1, although due to the uncertainty around the length of this maximum treatment duration, the impact of relaxing this assumption is tested in a scenario in Section B.3.8.3.

Following the key previous appraisals in Table 20, and the NICE reference case perspective of direct costs to the NHS and Personal Social Services (PSS), the expected dose intensity and number of planned treatments received is considered in the economic analysis, to accurately predict the treatment cost implications of each treatment strategy to NHS England. The approach to this is described in Section B.3.5.1.

B.3.3. Clinical parameters and variables

Data from intermediate- and poor-risk patients in CheckMate 214 are pivotal in informing assumptions in the economic model generally, and its clinical parameters and variables specifically. The following clinical outcomes were assessed to directly inform the economic model:

- OS
- IRRC-assessed, RECIST-defined ORR (CR or partial response [PR])
- IRRC-assessed, RECIST-defined PFS
- TTD
- Dose delays and interruptions (reported in Section B.3.5.1)
- HRQL (reported in Section B.3.4.1)
- TRAEs (reported in Section B.3.4.3)

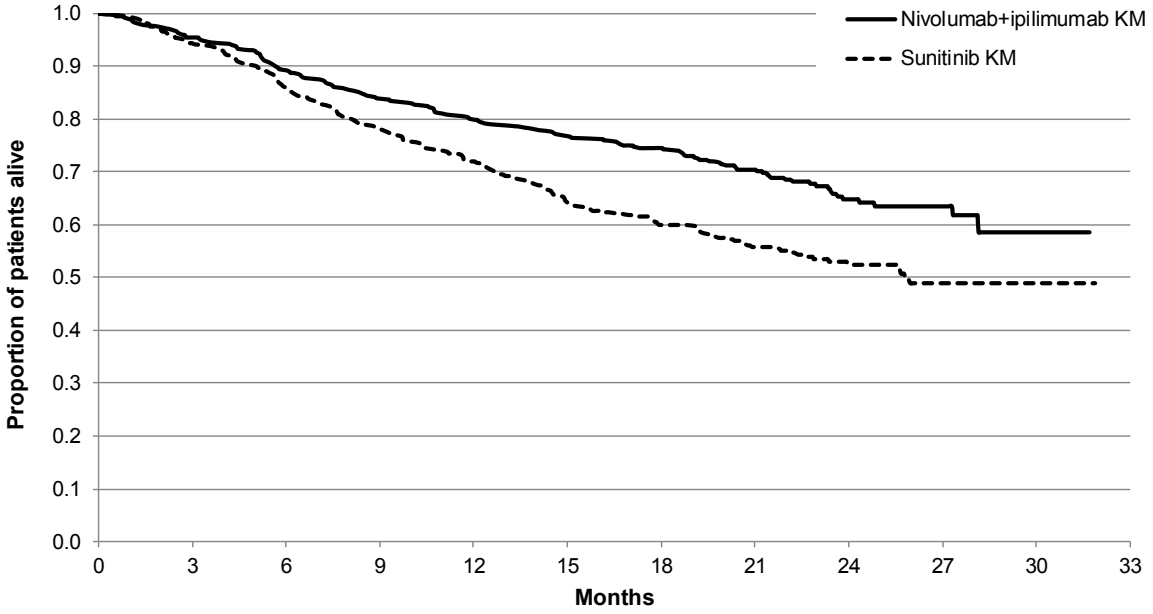
Parametric survival analyses of CheckMate 214 OS, PFS and TTD data inform the proportions of patients in each model health state in each cycle in the NIVO+IPI and sunitinib arms of the economic model. To inform the proportions of patients in each health state in each cycle of the pazopanib model arm, results from OS and PFS NMAs reported in Section B.2.9 and data from elsewhere in the literature are used to inform relative effectiveness estimates. The body of emerging and longer-term OS evidence for nivolumab, ipilimumab and other immunotherapies in RCC and similar carcinomas are used to inform assumptions about long-term immunotherapeutic survival implications for a minority of patients.

The remainder of Section B.3.3 describes the methodology and results of parametric survival analyses to capture and extrapolate OS, PFS and TTD data from CheckMate 214 over a lifetime horizon, the incorporation of NMA results and other assumptions to populate clinical parameters for pazopanib, and the data-driven approach to capture an anticipated immune checkpoint inhibitor-driven long-term survival benefit for a minority of patients who receive immunotherapeutic agents.

B.3.3.1. Overall survival

Figure 15 shows the KM data for intermediate-/poor-risk patients in CheckMate 214; Table 21 shows the underlying number at risk, over time.

Figure 15: CheckMate 214 overall survival – intermediate-/poor-risk patients, Kaplan–Meier curves



Key: KM, Kaplan–Meier.

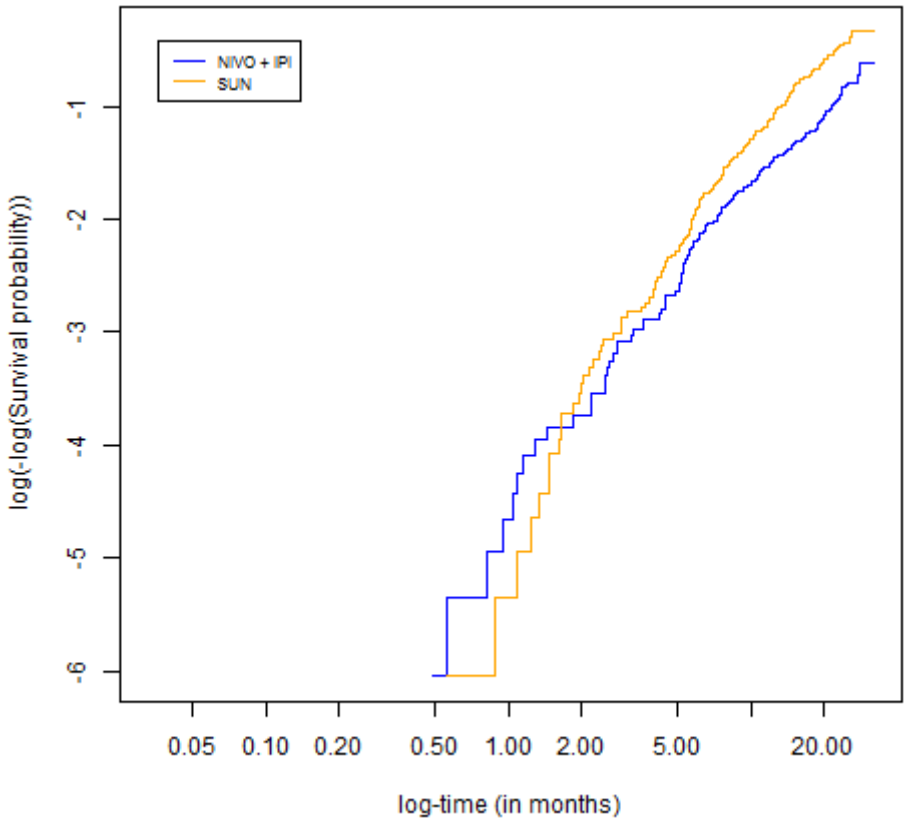
Table 21: CheckMate 214 overall survival – intermediate-/poor-risk patients, number at risk

Months											
0	3	6	9	12	15	18	21	24	27	30	33
NIVO+IPI, number at risk											
425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib, number at risk											
422	387	352	315	288	253	225	179	89	34	3	0
Key: NIVO+IPI, nivolumab + ipilimumab.											

Owing to incomplete data, parametric model extrapolation was used to capture OS over a lifetime horizon, following guidance in NICE Decision Support Unit Technical Support Document (DSU TSD) 14.[69] An assumption of proportional hazards (PH) across the two treatment arms of CheckMate 214 was first tested, to assess whether survival analysis stratified by treatment group was appropriate. Figure 16 shows the log-cumulative hazard plot for OS in intermediate-/poor-risk patients in CheckMate

214. This plot, the KM plot in Figure 15 and a Grambsch–Therneau correlation test were used to assess the plausibility of a PH assumption.[70] The Grambsch–Therneau correlation test did not reject the PH assumption (p=0.516), but the crossing of the log-cumulative hazards in Figure 16 and separating of KM and log-cumulative hazard curves after 3 months suggest a PH assumption may be weak. In addition, from a clinical perspective, the different mechanisms of action of NIVO+IPI and sunitinib (two different immunological response-targeting antibodies in combination versus a VEGFR TKI, respectively) do not suggest that the PH assumption will hold in the long-term. Survival analyses were therefore run on both (i) the OS data stratified by treatment arm, and (ii) the OS data unstratified by treatment arm.

Figure 16: Log-cumulative hazard plot, CheckMate 214 overall survival – intermediate-/poor-risk patients



Key: NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib.

The economic model contains the full suite of survival analyses, and the functionality to test economic analysis results for the range of different survival analysis options.

Given the questionable nature of a PH assumption for OS, only survival analyses performed using data stratified by treatment arm are considered for the remainder of Section B.3.3.1.

Seven parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, Gamma and generalised Gamma) were fitted to the CheckMate 214 OS data. Due to the good fit to the data, no further survival models were required.

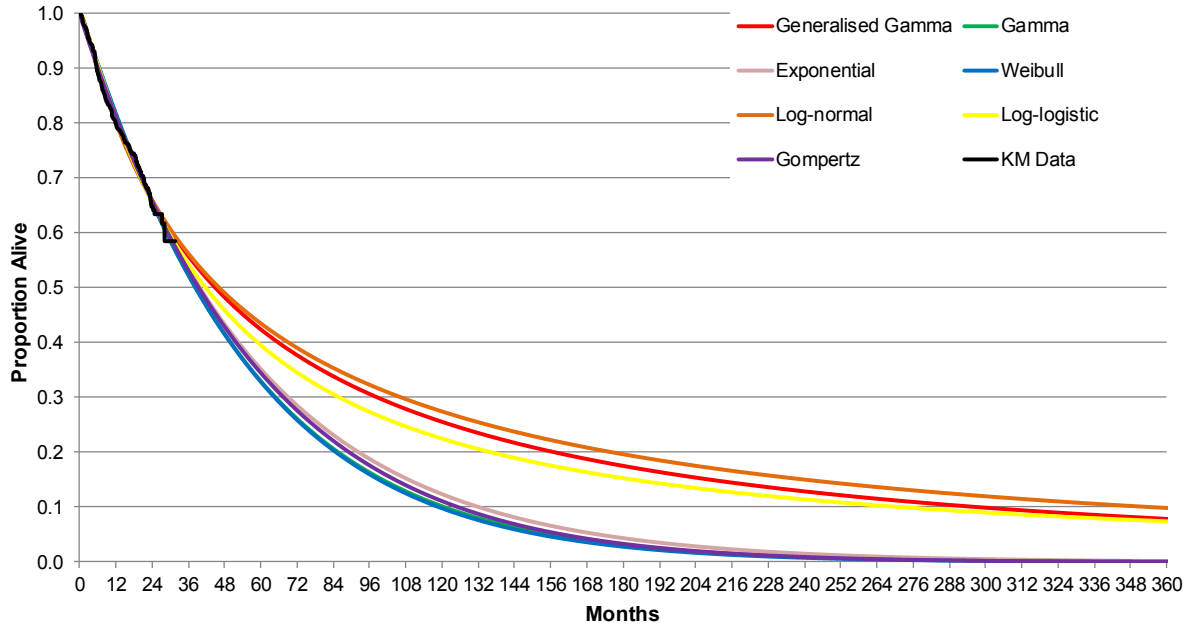
Goodness of fit was assessed by visual assessment of model curves versus KM data, shown in Figure 17 and Figure 18, and using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, shown in Table 22.

Table 22: AIC and BIC statistics for independent curve fits to CheckMate 214 OS data

	NIVO+IPI		Sunitinib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1416.4	1420.4	1741.4	1745.4
Gamma	1417.6	1425.7	1738.4	1746.5
Generalised Gamma	1416.5	1428.6	1728.8	1741.0
Gompertz	1418.4	1426.5	1743.4	1751.5
Log-logistic	1416.6	1424.7	1732.9	1741.0
Log-normal	1414.6	1422.7	1727.3	1735.4
Weibull	1417.8	1425.9	1739.9	1748.0

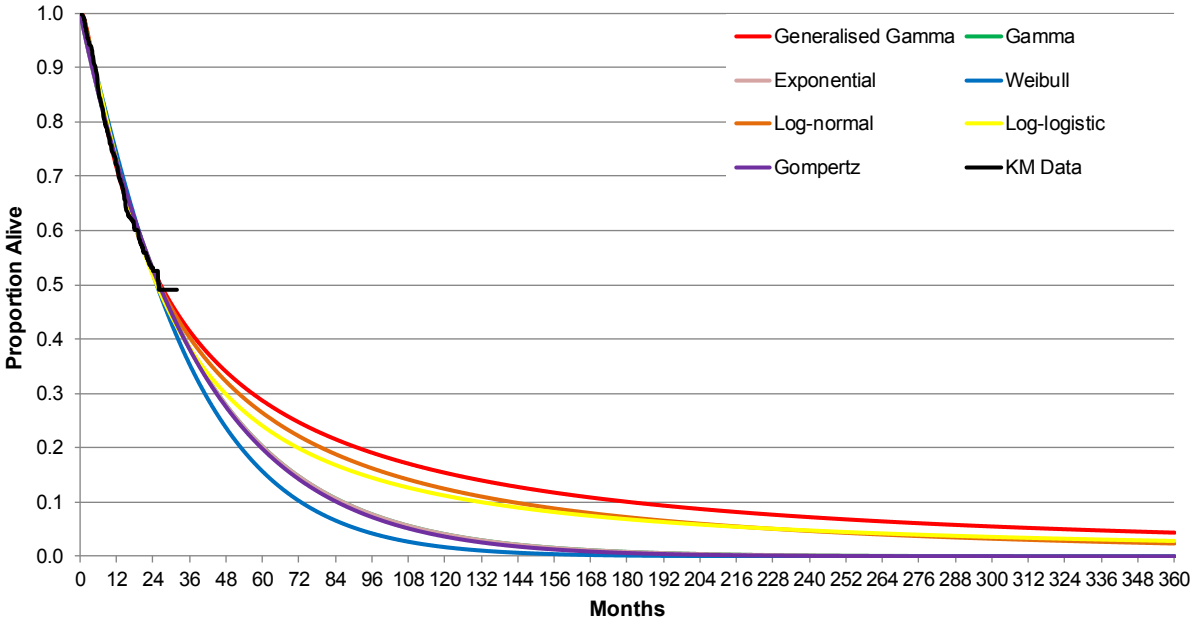
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.
Notes: Darker shades of green indicate better fit.

Figure 17: Parametric model fits to stratified OS data from CheckMate 214, NIVO+IPI arm



Key: KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.

Figure 18: Parametric model fits to stratified OS data from CheckMate 214, sunitinib arm



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

While all parametric curves provide a good visual fit to KM data, the log-normal model provided the best statistical fit to each stratified dataset. However, given the immaturity of the OS data and different extrapolation projections of each parametric model, parametric model selection was based primarily on the clinical plausibility of projected OS over the lifetime horizon.

The plausibility of the different projections was assessed by a practicing NHS England Medical Oncologist, Dr James Larkin, Consultant Medical Oncologist at Royal Marsden NHS Foundation Trust, in a 13 December 2017 interview. A meeting report, reviewed and approved by those present, is included as a reference as part of this submission.[46] Dr Larkin encouraged the use of final results from the sunitinib global expanded access study of 4,543 RCC patients reported by Gore and colleagues[53], to validate sunitinib extrapolations in this appraisal, but estimated that 15–20% survival at 5 years may be expected for first-line intermediate-/poor-risk patients who receive sunitinib as a first-line treatment agent for advanced RCC.[46] The log-logistic model fit to sunitinib CheckMate 214 intermediate-/poor-risk OS data in Figure 18 more closely matches this clinical expectation than the better-fitting log-normal model, while showing good fit to the observed data.

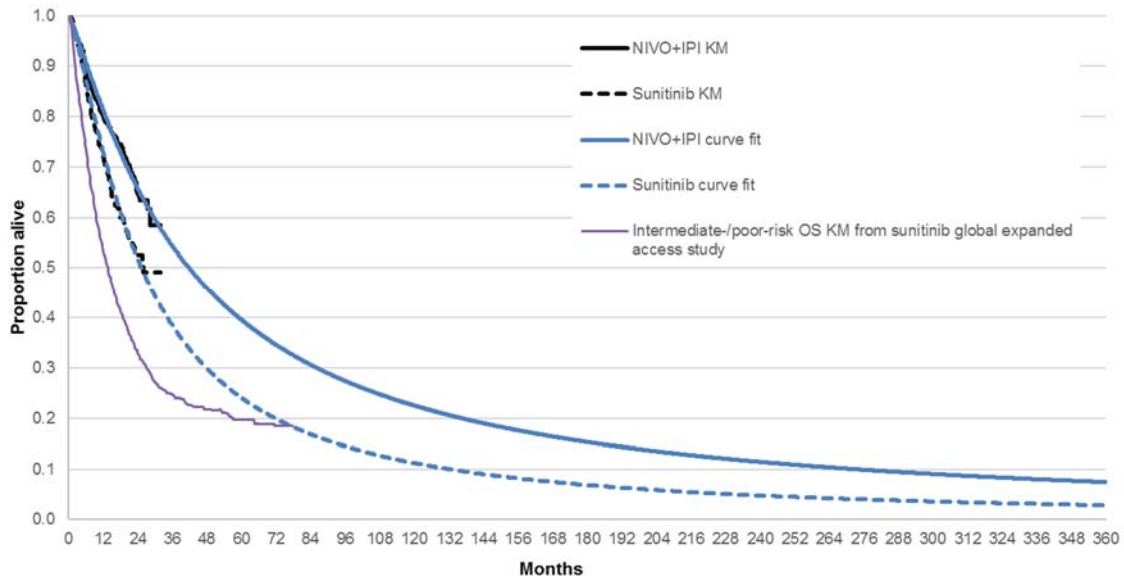
While long-term real-world evidence for NIVO+IPI in RCC patients is lacking, Dr Larkin could only estimate that 5-year CheckMate 214 intermediate-/poor-risk NIVO+IPI patient survival will likely be between 35% and 45%.[46] Overall, using log-logistic model fits to each arm of the stratified OS dataset provides both good statistical fit to observed data and conservative inference for long-term relative survival. In addition, the shape assumptions of these model fits are consistent with expectations for a treatment pathway involving immunotherapies, for immunogenic disease. With shape parameters >1, the models imply initially increasing, then decreasing hazard of death over time,[69] consistent with expectations for response-driven survival prospects, discussed in Section B.3.3.2.

Figure 19 shows log-logistic model fits to (i) NIVO+IPI and (ii) sunitinib arms of intermediate-/poor-risk CheckMate 214 OS KM data, alongside KM data from Gore *et al.*[53], who reported OS KM figures stratified by IMDC prognostic risk categories. To incorporate Gore *et al* data into Figure 19, they were first digitised by the method of Guyot *et al*.[38] An intermediate-/poor-risk KM curve was generated from the

digitised versions of the intermediate- and poor-risk OS KM curves presented by Gore *et al.*, weighted by the relative proportions of intermediate- and poor-risk patients in the expanded access study.[53]

The comparability of the expanded access sunitinib study versus CheckMate 214 comparator arm data is severely limited by the different patient characteristics and backgrounds across the two datasets; most notably, 78% of patients in the expanded access study had received prior systemic therapy.[53] In addition, patients in the expanded access study did not have the opportunity to receive nivolumab monotherapy as subsequent therapy. As such, the superior outcomes for CheckMate 214 intermediate-/poor-risk sunitinib patients illustrated in Figure 19 are explicable. Two notable features are the flattening of the curve beginning around Year 3 and the intersection with the log-logistic CheckMate 214 comparator data extrapolation around 5 years.

Figure 19: Visual summary of base case (log-logistic model) OS fits to CheckMate 214 data, and comparison to digitised sunitinib expanded access study data[53]



Key: KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival.

In TA417, evidence in support of an immunotherapeutic survival benefit for a proportion of patients treated with nivolumab led to the committee's willingness to

"*consider better predictions of survival in its decision making*"[62], as documented in Table 20. The implications for OS projections in this appraisal for both patients treated with NIVO+IPI as a first-line treatment for advanced RCC, and for patients treated with sunitinib or another VEGFR TKI first-line and subsequently treated with nivolumab monotherapy as a second-line strategy, are considered and set out in Section B.3.3.2.

To consider the OS of pazopanib in the model, the OS for patients receiving pazopanib instead of sunitinib or NIVO+IPI is assumed to be equivalent to the estimated OS for patients receiving sunitinib. This simplifying assumption was validated as sensible by Dr Larkin on 13 December 2017,[46] and is driven by precedent and evidence:

- Final analysis results from the COMPARZ trial:
  - ITT HR for death with pazopanib versus sunitinib, 0.92; 95% CI (0.79, 1.06); p=0.24 by a stratified log-rank test[39]
  - MSKCC intermediate-risk subgroup HR for death with pazopanib versus sunitinib, 0.90; 95% CI (0.74, 1.09)[39]
  - MSKCC poor-risk subgroup HR for death with pazopanib versus sunitinib, 0.85; 95% CI (0.56, 1.28)[39]
- Conclusions from the ITC reported in Section B.2.9. Due to a lack of data, the base case ITC did not include comparison to pazopanib; OS data stratified by risk status are not available for pazopanib (and not using IMDC criteria for any dataset other than CheckMate 214).
- Previously conducted ITC for TA215 showed comparable efficacy between pazopanib and sunitinib OS (HR for death with pazopanib versus sunitinib 0.969; 95% CI 0.359–2.608)[26]
- Committee- and Evidence Review Group (ERG)-preferred assumptions in TA417, in which axitinib patient OS, PFS and utility was assumed equal to everolimus patient OS, PFS and utility, in favour of ITC estimates and axitinib patient-reported EQ-5D 3-level questionnaire (EQ-5D-3L) [59, 62]

B.3.3.2. Long-term survival implications of immune checkpoint inhibitor treatment of RCC

In preparation for TA417 submission in early 2016, to ensure any necessary assumptions in the economic model were clinically sound prior to submission, BMS sought advice from Dr James Larkin and two further NHS Clinical Oncologists treating patients with advanced RCC within the NHS in England or Wales. One of the key aims of these meetings was to understand the plausibility of different survival analysis extrapolations, beyond available data from CheckMate 025; the advice received had important implications for decision makers.

When asked to review parametric model projections for nivolumab patient OS, the following responses were recorded: the first oncologist interviewed reported expectation of an "*immune-response 'tail on the curve', in line with that seen with nivolumab for patients in melanoma"*[71]; the second expressed similar thoughts[71]; and the third noted the difficulty of predicting long-term OS accurately in RCC, in comparison to melanoma, but highlighted that immunotherapeutic treatments have been shown to affect survival after treatment stops, citing evidence for ipilimumab therapy in melanoma patients.[71] The implication was that extrapolations from parametric model fits to CheckMate 025 OS data were not able to show the expected extrapolation for nivolumab patients.

This information led to further company research and efforts to understand the breadth of evidence on long-term survival and further consultation with two of the three NHS Clinical Oncologists consulted.[72] Dr Larkin and Professor John Wagstaff, Deputy Clinical Director at the South West Wales Cancer Research Institute, Swansea, were interviewed separately and asked five pre-defined questions to elicit their survival expectations for previously treated RCC patients who receive nivolumab, beyond CheckMate 025 OS KM data. These five questions and responses, first shown as Table 3 of the company's response to ACD1 in TA417, are shown in Table 23. Based on conservative interpretation of these responses, scenario analyses were provided to the TA417 Committee, assuming a 50% probability that nivolumab patients who were projected to survive to (i) 3 years and (ii) 5 years would have similar risk of death to age-matched general population data.[73]

Table 23: NHS Clinical Experts' responses to five questions on long-term survival for patients similar to those in CheckMate 025

Pre-defined interview question	Dr James Larkin Consultant Medical Oncologist, Royal Marsden NHS Foundation Trust	Professor John Wagstaff Professor of Medical Oncology, The College of Medicine, Swansea University
1. Do you expect an immunotherapeutic survival plateau effect for RCC nivolumab patients who achieve long-term survival, and if so, why?	Yes, I expect a survival plateau for nivolumab-treated patients with mRCC. RCC is classified as an immunogenic disease, which is similar to melanoma. There is no reason to suppose that the outcomes observed will be any different in one or the other.	Yes, I would expect there to be a survival plateau, similar to the effect seen with immunotherapies in melanoma. This, however, would be a lower plateau, given the relative response rates observed.
2. Do you feel that the survival curve in Figure 1 under-predicts long-run survival for CheckMate 025 patients who survive beyond data collection? [Figure 1 is Figure 28 of the Company Submission – base case survival curve fits to CheckMate 025 Kaplan–Meier data]	Yes, that's correct. The curve presented in Figure 1 does not have an inflection point where you would expect one to be (between years 1 and 5), [and] therefore it does not demonstrate a typical tail as that which has been observed in similar melanoma patients. This survival curve is likely to underestimate the true benefit of nivolumab.	Yes, I agree. This model does under-predict what we will see in reality. The expectation is that sustained remissions will be seen with nivolumab-treated mRCC patients, and so there will be a plateau to the survival curve – I do not expect this line to reach 0.
3. Do you expect the immunotherapeutic survival plateau to allow patients who reach this stage to have survival rates similar to the general population?	Yes, patients that reach this phase in the curve would have a similar survival rate to those in the general population.	Yes, this makes sense – however, it should be noted that this model depicted above does not represent what a true plateau should look like anyway. In my experience, given that 70% of patients are likely to experience a remission, it would lead to the estimation of around 20% of patients comprising the plateau phase of the curve. This pattern would be similar to the long-term survival curve seen in melanoma patients treated with nivolumab and ipilimumab.

Pre-defined interview question	Dr James Larkin Consultant Medical Oncologist, Royal Marsden NHS Foundation Trust	Professor John Wagstaff Professor of Medical Oncology, The College of Medicine, Swansea University
4. How long after treatment initiation would you expect the immunotherapeutic survival plateau to become visible if CheckMate 025 patients could be observed indefinitely?	As there is a paucity of mature data in these patients with this treatment in RCC, it would be difficult to give a certain numerical answer. However, given the mechanism of action of this immunotherapy drug, as well as similar-acting agents, the expectation would be that a plateau would be observed approximately 2–3 years after initiation of treatment.	We expect a similar impact to those patients with melanoma treated with nivolumab. Thus, a plateau potentially would be seen around 3 years. From this point it would be expected that the patients would have a similar death rate to those in the general population (as mentioned earlier).
5. What in your opinion is the likelihood, or probability, that the immunotherapeutic survival plateau you expect for CheckMate 025 would be seen, if it were possible to observe CheckMate 025 patients indefinitely?	Yes, that is correct – it is likely that there would be a survival plateau observed.	Yes, as stated previously, this is very likely.
Key: mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma;		

The expectations reported in Table 23 were based on sound biological rationale, encompassing the immunogenic nature of RCC and the immunomodulatory mechanisms of nivolumab.[73] While the CheckMate 025 data were at the time of TA417 too immature to demonstrate a survival plateau, clinical experts' expectations were explained and supported through follow-up data from safety and efficacy studies and evidence for nivolumab monotherapy in advanced melanoma, and for ipilimumab in advanced melanoma, including:[73]

- OS evidence for nivolumab in previously treated RCC patients in Phase I/II trials (34% and 20% at latest follow-up of 5 years in CheckMate 003[45] and CheckMate 010 (data on file), respectively, in patient groups in which ORRs of 24.3%[74] and 21.6%[45] were observed)
- The immunogenic nature of advanced RCC (first demonstrated in trials of IL-2 cytokine immunotherapy where a proportion of patients achieved long-term response)[3, 75-77]
- The immunotherapeutic mechanism of action of nivolumab[77]
- OS evidence for nivolumab in previously treated melanoma (35% at latest follow-up of 5 years, CheckMate 003)[78]
- OS evidence for ipilimumab in melanoma (plateau from 21% at 3 years with follow-up data for up to 10 years where OS remains above 17%, pooled analysis of 10 studies including two Phase III studies)[44]

This body of evidence is directly relevant to this appraisal. Furthermore, more mature data from CheckMate 025 are now available to inform and validate survival plateau assumptions herein. Figure 20 shows OS KM data from the June 2017 data-cut of CheckMate 025 (minimum follow-up ~38 months), presented at the 16th International Kidney Cancer Symposium in November 2017.[79] At 36 months, before heavy censoring indicating those who entered the study later in the enrolment period, the OS rate for nivolumab patients is 39% (higher than the TA417 base case parametric model extrapolation of <38% at 36 months)[59], and OS KM data appear to be showing signs of tending towards the expected plateau.

Figure 20: [redacted][79]

[redacted]

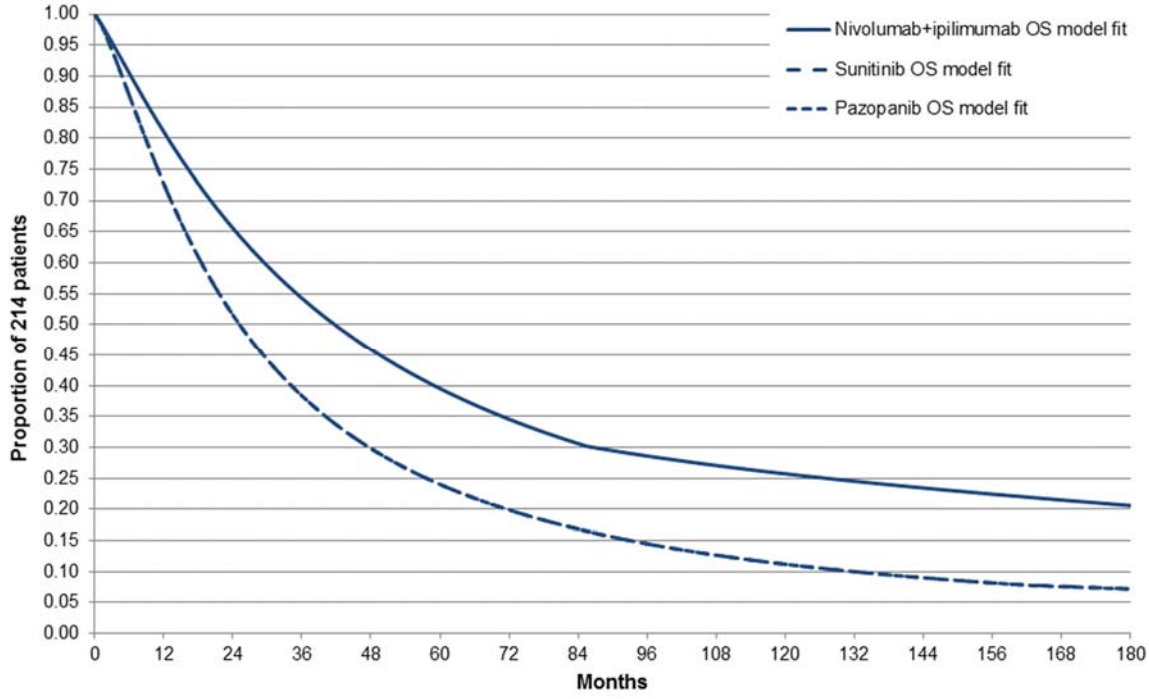
Further NHS Oncologist insights were sought in preparation for this submission; in anticipation of narrow timelines between CheckMate 214 results, EMA submission and NICE submission deadlines, interviews were first held in August 2017, prior to results from CheckMate 214 emerging. The two NHS Clinical Oncologists who informed Table 23 responses, Dr James Larkin and Professor John Wagstaff, were again separately interviewed, primarily to gain their insight into the 2017 NHS care pathway and the potential implications of ongoing and planned NICE appraisals.[54] In the absence of results from CheckMate 214, expectations for the effectiveness of NIVO+IPI for untreated, advanced RCC patients were based on evidence for and NHS experience of nivolumab and ipilimumab as monotherapies in RCC and melanoma patients, and in combination in melanoma patients. There was an expectation that for a proportion of patients who receive NIVO+IPI an immunotherapeutic survival tail would be evidenced, with particular reference to the positive 3-year OS results for NIVO+IPI in advanced melanoma patients in CheckMate 067, the relationship between ORR and 3-year OS in these data, and the depth of response observed for some patients in CheckMate 067 and CheckMate 025.[54]

In the December 2017 model validation meeting, Dr Larkin reiterated that immunotherapeutic survival is contingent on durable response.[46] The proportion of durable responders in the latest data (7 August 2017 database lock) from CheckMate 214 intermediate-/poor-risk patients who received NIVO+IPI was therefore used to inform immunotherapeutic survival assumptions. Of the 425 intermediate-/poor-risk patients randomised to IPI+NIVO, 177 (41.6%) achieved a response, as reported in Section B.2.6.1. Of these 177 patients, 128 were still responding at last data entry in the August 2017 dataset, as also reported in Section B.2.6.1. These 128 patients comprise 72.3% of the 177 patients who achieved a response, and 30.1% of the 425 patients randomised to NIVO+IPI.

In the base case analysis, the durable responders in the NIVO+IPI arm of CheckMate 214, 30.1% of patients, are assumed to have survival similar to the general population. For balance, those first-line sunitinib patients predicted to have a durable response to nivolumab monotherapy as a second-line immune checkpoint inhibitor treatment are also assumed to have general population-equivalent survival prospects. Of 410 patients randomised to nivolumab in CheckMate 025, 103 achieved a response. For simplicity, the proportion of responders who prove to be durable responders is assumed to be consistent with NIVO+IPI for first-line intermediate-/poor-risk patients, and 72.3% of patients in the model who are estimated to receive and respond to second-line nivolumab treatment are assumed to achieve a durable response. This gives a durable response rate of 18.2% for nivolumab patients at second-line, which is applied to the proportion of patients receiving nivolumab at second-line.

The implications for survival prospects in the economic model are illustrated by Figure 21. Of course, an immune-response survival for durable responders is an expectation rather than a certainty. As such, the probability of an immunotherapeutic survival plateau for durable responders is included as a variable in the model. In the base case, a probability of 0.5 is assumed. If an immunotherapeutic survival benefit for durable responders is likely, this probability estimate can be considered conservative. The sensitivity of model results to alternative long-term survival assumptions is tested in sensitivity and scenario analyses in Section B.3.8.

Figure 21: Visual summary of base case OS assumptions, including durable responder immunotherapeutic survival assumption

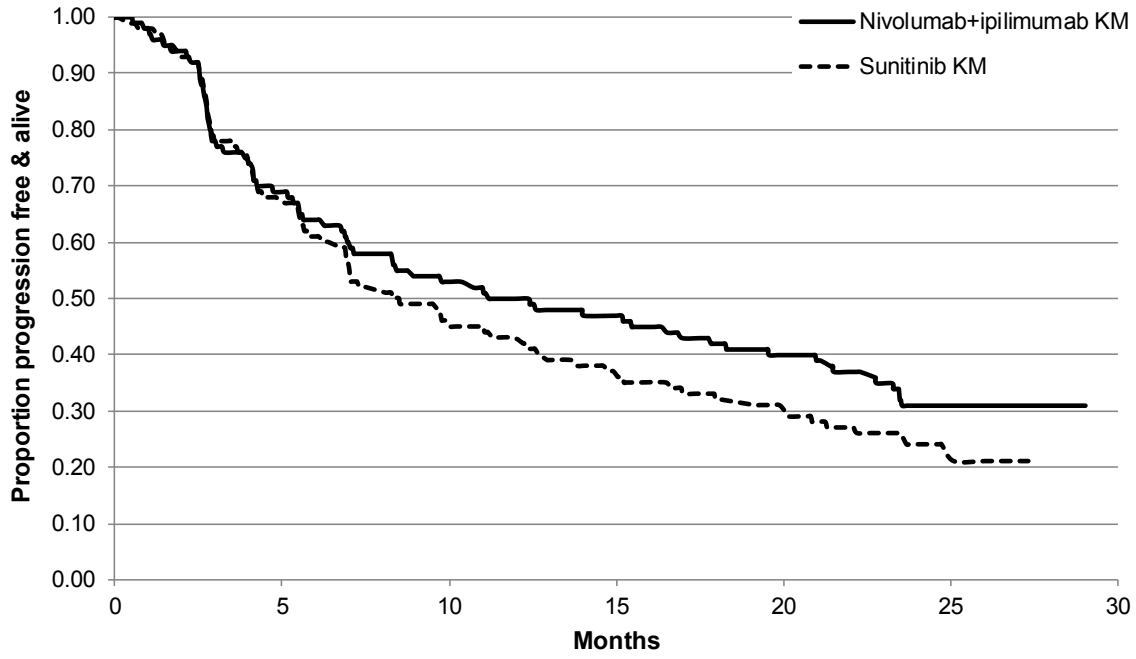


Key: KM, Kaplan–Meier; OS, overall survival.

B.3.3.3. Progression-free survival

Figure 22 shows the KM data for intermediate-/poor-risk patients in CheckMate 214, and Table 24 shows the number of patients at risk, over time.

Figure 22: CheckMate 214 progression-free survival – intermediate-/poor-risk patients, Kaplan–Meier curves



Key: KM, Kaplan–Meier.

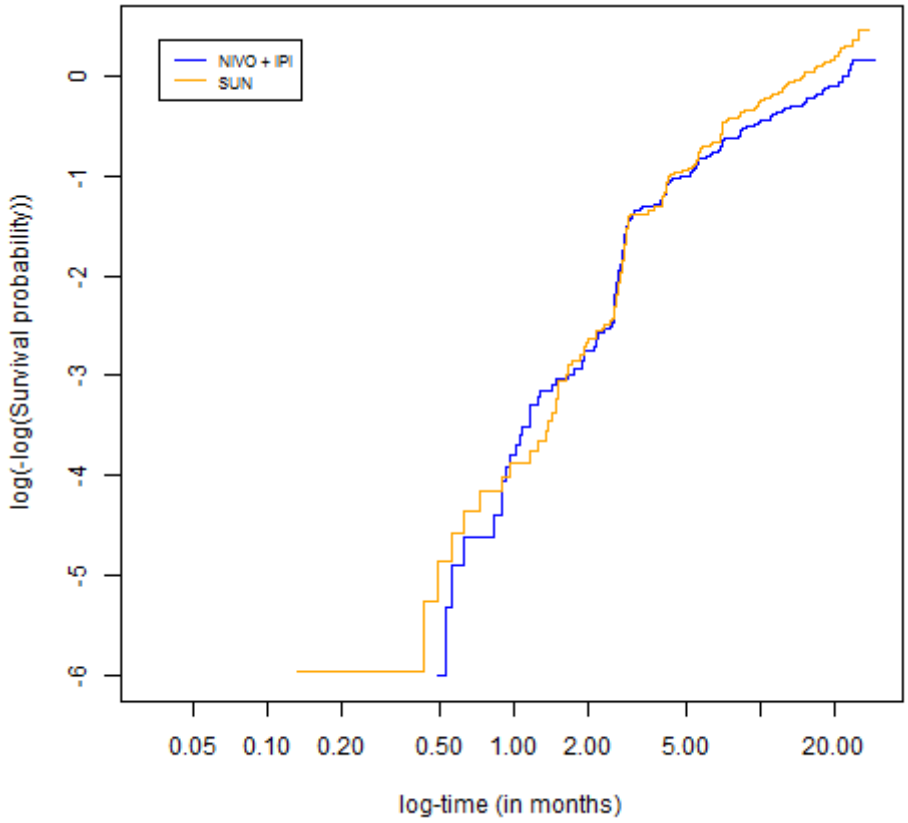
Table 24: CheckMate 214 progression-free survival – intermediate-/poor-risk patients, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI										
425	304	233	187	163	149	118	46	17	3	0
Sunitinib										
422	282	191	139	107	86	57	33	11	1	0
Key: NIVO+IPI, nivolumab + ipilimumab.										

Although the PFS data are more complete than the OS data, they remain incomplete, and parametric extrapolation was necessary.[69] The assumption of PH was first tested to assess whether survival analysis stratified by treatment group was appropriate. The log-cumulative hazard plot, the KM plot and the Grambsch–Therneau correlation test were again used to test the PH assumption.[70] In the log-cumulative hazard plot, the curves cross several times in the first 5 months before

separating (Figure 23; also shown in the KM plot, Figure 22), which would suggest that the PH assumption does not hold. Similar to OS, the Grambsch–Therneau correlation test did not reject the PH assumption (p=0.103), but with the differing mechanisms of action of the two treatments, we would not expect the PH assumption to hold. Survival analyses were therefore run on both (i) the PFS data stratified by treatment arm, and (ii) the PFS data unstratified by treatment arm.

Figure 23: Log-cumulative hazard plot, CheckMate 214 progression-free survival – intermediate-/poor-risk patients



Key: NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib.

As with OS, the economic model contains the full suite of survival analyses, and the functionality to test economic analysis results for the range of different PFS analysis options. However, given the questionable nature of a PH assumption for PFS, only survival analyses run on data stratified by treatment arm are considered for the remainder of Section B.3.3.3.

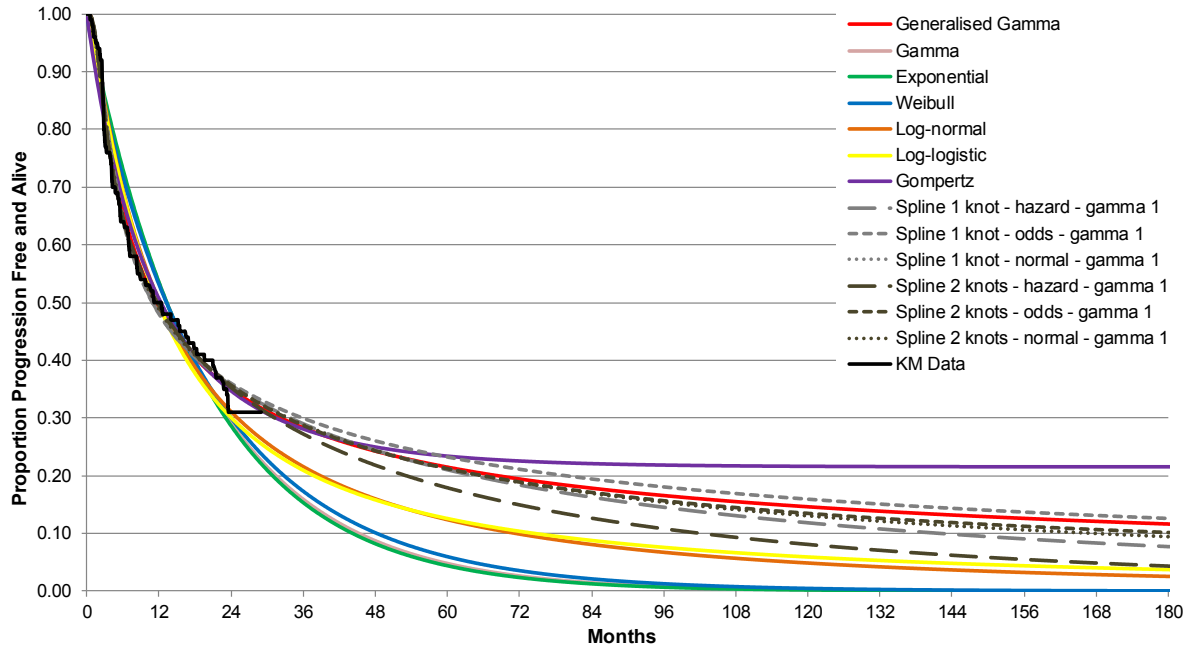
Curves were fitted to the CheckMate 214 intermediate-/poor-risk PFS data using the same seven standard parametric models considered for OS data (exponential, Weibull, Gompertz, log-logistic, log-normal, Gamma and generalised Gamma)[69] and, given data characteristics of PFS, in particular the sharp initial fall in PFS after approximately 2 months, and subsequent flattening of the curve afterwards (clearest in Figure 19), six spline-based models (hazard, normal and odds models, each using either 1 or 2 knots, as used in TA417[59]). Goodness of fit was assessed by visual assessment of model curves versus KM data, shown in Figure 24 and Figure 25, and using AIC and BIC statistics, shown in Table 25.

Table 25: AIC and BIC statistics for independent curve fits to CheckMate 214 PFS data

	NIVO+IPI		Sunitinib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Cubic spline model: 1 knot hazard	1742.9	1755.1	1644.7	1656.8
Cubic spline model: 1 knot normal	1742.1	1754.3	1652.3	1664.5
Cubic spline model: 1 knot odds	1742.2	1754.3	1644.7	1656.9
Cubic spline model: 2 knots hazard	1740.0	1756.2	1647.2	1663.4
Cubic spline model: 2 knots normal	1744.8	1761.1	1648.0	1664.2
Cubic spline model: 2 knots odds	1741.4	1757.6	1647.0	1663.2
Exponential	1805.5	1809.6	1688.1	1692.2
Gamma	1807.3	1815.4	1685.9	1694.0
Generalised gamma	1746.9	1759.0	1654.1	1666.2
Gompertz	1789.0	1797.1	1686.5	1694.5
Log-logistic	1781.1	1789.2	1661.3	1669.4
Log-normal	1765.0	1773.1	1654.2	1662.3
Weibull	1805.8	1813.9	1688.8	1696.9

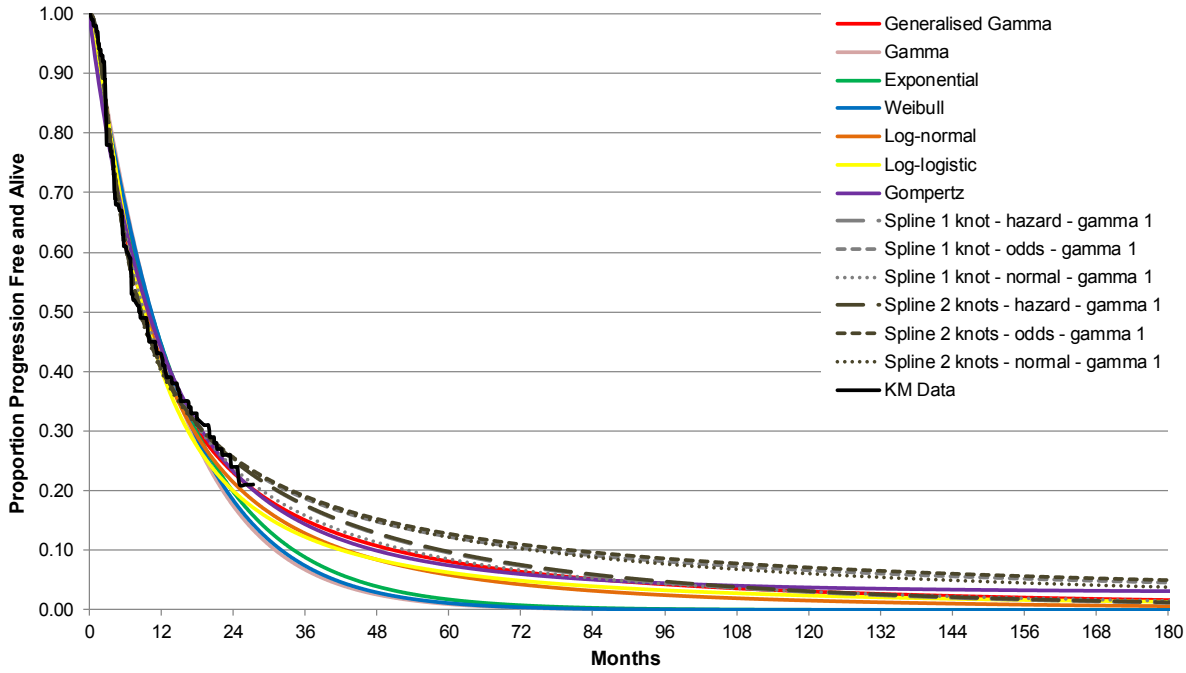
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival.
Notes: Darker shades of green indicate better fit.

Figure 24: Parametric model fits to stratified PFS data from CheckMate 214, NIVO+IPI arm



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

Figure 25: Parametric model fits to stratified PFS data from CheckMate 214, sunitinib arm



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

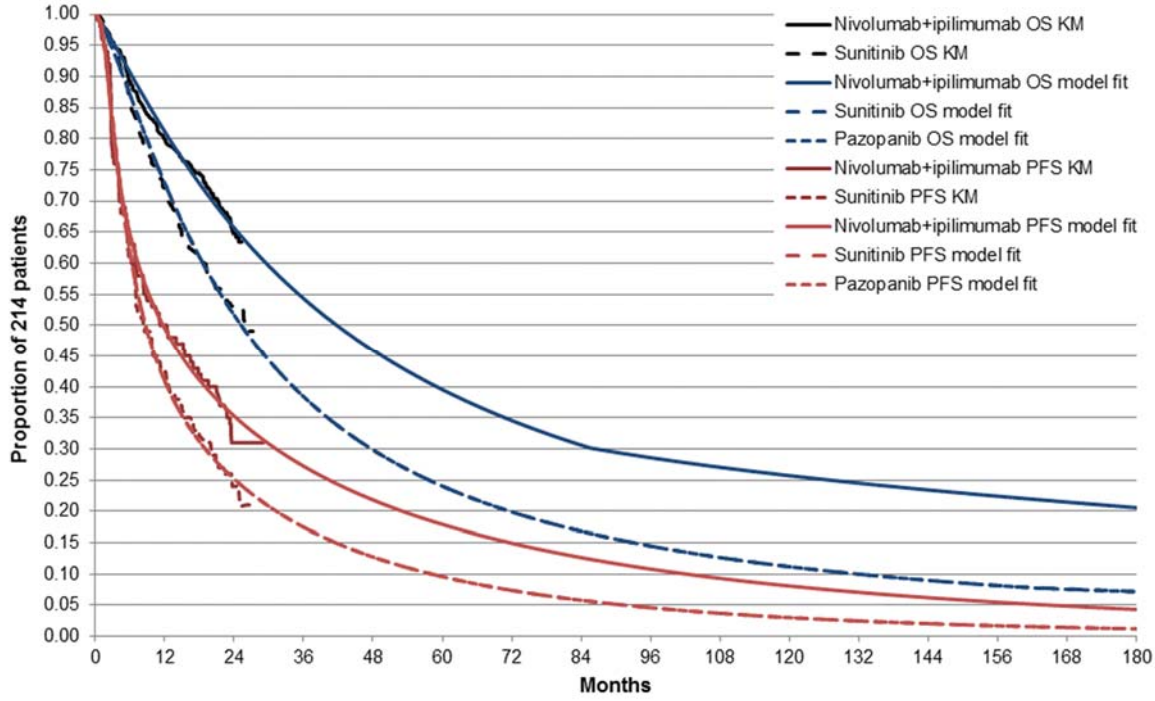
Standard parametric models did not provide a particularly good fit to the data, either visually (Figure 24 and Figure 25) or statistically (Table 25). The steep drop in PFS observed may be due to the timing of the first CT or MRI scan, which is given 12 weeks (+/- 1 week) from randomisation and may indicate a subgroup of patients with poorest prognosis who are defined in accordance with RECIST criteria as progressing at point of first scan. In contrast, the flat tail at the end may represent those patients with better prognosis and those whose disease stabilises following the initial tumour flare seen on the scan.

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 NIVO+IPI PFS, spline-based models provide a better visual fit to the observed data.

For NIVO+IPI, the best-fitting model was the spline odds 2-knot model according to AIC. For sunitinib, the spline hazard 1-knot model was the best fitting according to AIC and BIC. However, given the immaturity of the PFS data and different extrapolation projections of each parametric model (although to a lesser extent than the OS projections), parametric model selection considered the clinical plausibility of projected PFS over the lifetime horizon.

The base case economic analysis is underpinned by a spline 2-knot hazard model fit to the NIVO+IPI intermediate-/poor-risk CheckMate 214 PFS data and a spline 1-knot hazard model fit to the sunitinib intermediate-/poor-risk CheckMate 214 PFS data; these are shown alongside base case parametric OS extrapolations in Figure 26.

Figure 26: Visual summary of base case PFS and OS projections and CheckMate 214 KM data



Key: KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.
Note: OS model fits reflects the assumption of long-term immunotherapeutic effect described in Section B.3.3.2.

To consider the PFS of pazopanib in the model, the PFS for patients receiving pazopanib instead of sunitinib or NIVO+IPI is assumed to be equivalent to the estimated PFS for patients receiving sunitinib. As was the case for OS, this simplifying assumption is supported by precedent and evidence:

- Interim results from the COMPARZ trial (HR for progression or death on pazopanib versus sunitinib of 1.05; 95% CI [0.90, 1.22]; meeting predefined criterion for noninferiority)[5]
- The ITC reported in Section B.2.9 highlighted clear limitations in ITC to add to the conclusions from COMPARZ for the purpose of this appraisal. In particular, risk-stratified information for pazopanib PFS was only available in the subgroup of intermediate-risk patients. Results from four sets of analyses suggest no statistical differences between sunitinib PFS and pazopanib PFS.
- Previously conducted ITC for TA215 (HR for progression or death on pazopanib versus sunitinib of 0.949; 95% CI [0.575, 1.568])[26]

- Committee- and ERG-preferred assumptions in TA417, in which axitinib patient OS, PFS and utility was assumed equal to everolimus patient OS, PFS and utility, in favour of ITC estimates and axitinib patient-reported EQ-5D-3L[59, 62]

As a consequence of the partitioned survival model structure, PPS is defined as the difference between PFS and OS. A limit is built into the model whereby PFS cannot exceed OS; if PFS is estimated to be greater than OS at any time on any model arm, PPS is assumed to be zero, and PFS is assumed to be equal to OS.

B.3.3.4. Time to treatment discontinuation

Figure 27 shows the KM data for intermediate-/poor-risk patients in CheckMate 214, and Table 26 shows the number at risk, over time. Median TTD was [redacted] for NIVO+IPI patients and 6.2 months for sunitinib patients.

Figure 27: CheckMate 214 time to treatment discontinuation – intermediate/poor risk patients, Kaplan–Meier curves

Key: KM, Kaplan–Meier.

Table 26: CheckMate 214 time to treatment discontinuation – intermediate-/poor-risk patients, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI										
[redacted]										
Sunitinib										
416	302	209	153	118	101	69	40	17	13	0
Key: NIVO+IPI, nivolumab + ipilimumab.										

Although more complete than the OS and PFS data, the TTD data remain incomplete at the time of this analysis, and parametric modelling was used to estimate lifetime TTD across treatment arms.[69] PH was again first tested using the KM plot, the log-cumulative hazard plot and the Grambsch–Therneau correlation test, to assess whether survival analysis stratified by treatment group was appropriate.[70] The log-cumulative hazard curves and the KM curves cross between 3 and 4 months and then begin to separate (Figure 27 and Figure 28). In addition, the Grambsch–Therneau correlation test rejected the PH assumption ($p<0.001$); there is clear evidence that an assumption of PH across treatment arms would be inappropriate. For completeness, as for OS and PFS, survival analyses were run on both (i) the TTD data stratified by treatment arm, and (ii) the TTD data unstratified by treatment arm, and the full suite of analyses are available to test in the economic model. However, only curves fitted to stratified TTD data are considered for the remainder of Section B.3.3.4.

Figure 28: Log-cumulative hazard plot, CheckMate 214 time to treatment discontinuation – intermediate-/poor-risk patients

Key: NIVO+IPI, nivolumab + ipilimumab; SUN, sunitinib.

The standard parametric models fitted to OS and PFS data (exponential, Weibull, Gompertz, log-logistic, log-normal, Gamma and generalised Gamma)[69] were also fitted to TTD data, alongside six spline-based models (hazard, normal and odds models, using either 1 or 2 knots), reflecting the approach to model PFS in Section B.3.3.3. Goodness of fit was again assessed by visual assessment of model curves versus KM data, shown in Figure 29 and Figure 30, and using AIC and BIC statistics, shown in Table 27.

Table 27: AIC and BIC statistics for independent curve fits to CheckMate 214 TTD data

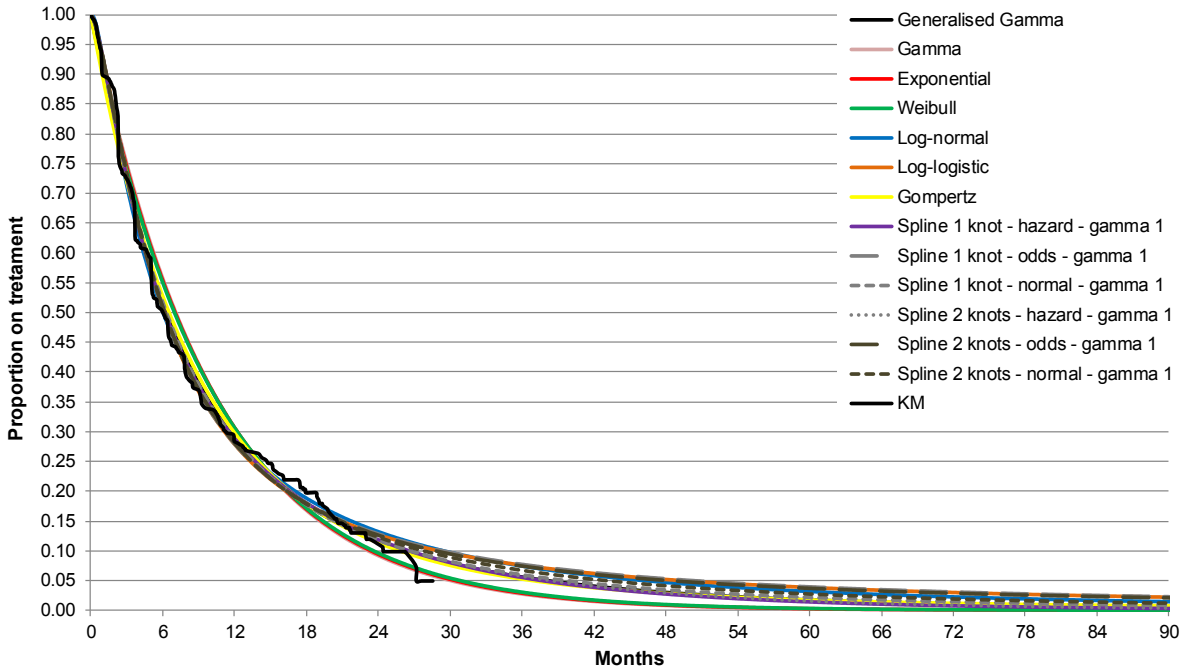
Model	NIVO+IPI		Sunitinib	
	AIC	BIC	AIC	BIC
Cubic spline model: 1 knot hazard	2263.0	2275.2	2367.8	2379.9
Cubic spline model: 1 knot normal	2257.7	2269.9	2370.8	2382.9
Cubic spline model: 1 knot odds	2257.0	2269.2	2371.0	2383.1
Cubic spline model: 2 knots hazard	2254.5	2270.7	2369.9	2386.1
Cubic spline model: 2 knots normal	2251.7	2267.8	2371.5	2387.6
Cubic spline model: 2 knots odds	2253.8	2270.0	2372.9	2389.0
Exponential	2323.6	2327.7	2383.6	2387.7
Gamma	2268.7	2276.8	2385.5	2393.5
Generalised gamma	2262.7	2274.9	2370.2	2382.3
Gompertz	2266.4	2274.5	2381.2	2389.3
Log-logistic	2259.5	2267.6	2369.1	2377.1
Log-normal	2283.0	2291.1	2373.3	2381.3
Weibull	2262.9	2271.0	2385.5	2393.6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; NIVO+IPI, nivolumab + ipilimumab; TTD, time-to-treatment discontinuation.
Notes: Darker shades of green indicate better fit.

Figure 29: Parametric model fits to stratified TTD data from CheckMate 214, NIVO+IPI arm

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

Figure 30: Parametric model fits to stratified TTD data from CheckMate 214, sunitinib arm



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

The spline models improved statistical fit over the standard parametric curves, with the spline normal 2-knot model the statistically best-fitting for NIVO+IPI and the spline hazard 1-knot model the statistically best-fitting for sunitinib. However, apart from the exponential model fit to NIVO+IPI TTD data and Gompertz and Weibull fits to sunitinib TTD data, standard parametric models provided good visual fits to the KM data.

Despite the relative maturity of the TTD data versus the PFS and OS data, the different long-term TTD implications of the different models tested for NIVO+IPI patients in particular highlight how opinion from the 13 December 2017 meeting with Dr Larkin was important alongside goodness-of-fit statistics to inform lifetime TTD extrapolations. However, Dr Larkin felt he could not choose between the models in an informed, data-driven manner. A more general discussion led Dr Larkin to opine that clinicians will consider treatment continuation for long-term responders when cumulative toxicity is considered to tip the balance of risk–benefit ratio of ongoing therapy.[46] [redacted]

[redacted]

From a patient perspective, staying on treatment for 5 years would be extremely demanding. This would require at least 210 hospital visits for treatment administration alone and due to being on treatment for a longer time, there is an increased risk of experiencing an adverse event. To reduce patient burden (and NHS resourcing), BMS believe patients would be treated for a maximum of 5 years. Latest data from CheckMate 010, showing [redacted] ([redacted]) remaining on nivolumab at 5 years, suggest the practical implication of a 5-year stopping rule is likely to be minimal. This assumption is incorporated into the model base case, although due to the uncertainty around the length of a stopping rule and the relevance for NHS England practice, the impact of this input is tested in a scenario in Section B.3.8.3.

Extrapolations for TTD alongside KM data and base case data for OS and PFS are summarised in Figure 31.

Figure 31: Visual summary of base case TTD, PFS and OS fits to CheckMate 214 data


[redacted]

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

Note: OS model fits reflects the assumption of long-term immunotherapeutic effect described in Section B.3.3.2.

For pazopanib, toxicity on treatment is understood to be less of an issue than for sunitinib. In COMPARZ, patients receiving pazopanib had greater median treatment duration (8.0 versus 7.6), fewer patients with treatment interruptions (44% versus 49%), and fewer patients with dose reductions (44% versus 51%), in comparison to patients receiving sunitinib.[5] As such, the assumptions made in the economic analysis for pazopanib TTD differ from those made for sunitinib TTD. In the economic analysis base case, the ratio between median TTD for sunitinib and pazopanib from COMPARZ (7.6 months sunitinib / 8.0 months pazopanib)[39] is applied as a HR to the sunitinib TTD curve shown in Figure 26, to generate a TTD curve for pazopanib.

Although the pazopanib model arm uses the same initial PFS and OS curves, due to long-term survival assumptions (from subsequent nivolumab), as well as subsequent treatment calculations, being dependent on patients discontinuing treatment (see Section B.3.3.2 and B.3.5.4, respectively), pazopanib provides marginally less LYs than sunitinib. As pazopanib patients stay on treatment for longer, fewer discontinue to become eligible for subsequent therapy, and therefore subsequent nivolumab. This means fewer pazopanib patients are predicted to receive a durable response with nivolumab, and subsequently fewer receive long-term immunotherapeutic benefit.

Figure 32: NIVO+IPI, sunitinib and pazopanib modelled curves for OS, PFS and TTD

Key: KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.
Note: OS model fits reflects the assumption of long-term immunotherapeutic effect described in Section B.3.3.2.

B.3.4. Measurement and valuation of health effects

For patients with advanced RCC, quality of life is known to be substantially affected by disease symptoms, including fatigue, lack of appetite, and symptoms from metastatic disease such as bone pain.[80, 81] Treatment-related factors are highly 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.[72] With a view to factoring these patient considerations into the economic appraisal as much as possible, this section sets out the data, methods and assumptions used to measure and value health effects.

B.3.4.1. Health-related quality-of-life data from clinical trials

The CheckMate 214 protocol specified patient completion of the EQ-5D-3L questionnaire: on Day 1 of Week 1 of each 6-week study cycle, also on Day 1 of

Week 4 of each study cycle for the first 6 months of the study, and at the first two follow-up visits (approximately 30 days and approximately 114 days after last dose).[82] The questionnaire was then scheduled to be completed by site every 3 months for the first 12 months and every 6 months thereafter, at survival follow-up visits.[82] Assessments are performed prior to any study-related procedures. The UK EQ-5D-3L tariff was used to estimate utility values from patient questionnaire responses.

To account for autocorrelation of patient HRQL responses, and to understand how and whether CheckMate 214 intermediate-/poor-risk patient HRQL was affected by (i) treatment received, (ii) treatment status and (iii) disease status, regression analyses were performed. A mixed model equation was specified to model intermediate- and poor-risk patient CheckMate 214 EQ-5D-3L utility as a function of progression status, treatment arm and treatment status, using subject as a random effect to account for repeated measures. A stepwise approach to model selection was used, starting with a model containing the intercept only. Next, one main effect at a time was added, and the model with the lowest AIC was retained. Finally, one main effect and associated interaction terms were added to this model, sequentially, and the model from these with the lowest AIC was retained as the best-fitting model. Results from this stepwise selection process are presented in Table 28. The final model, Model 5 in Table 28, captures patient EQ-5D-3L utility as a function of treatment arm, treatment status and the interaction between these two binary variables.

Table 28: Results from stepwise variable selection approach to mixed model analysis of CheckMate 214 intermediate-/poor-risk EQ-5D-3L utility data

	Estimate (SE), p-value						
Parameters/Fit statistics	Model 1: intercept only	Model 2: add Treatment Arm	Model 3: add Progression Status	Model 4: add Treatment Status	Model 5: add Treatment Arm to Model 4	Model 6: add Progression Status to Model 4	Model 7: add Progression Status to Model 5
Intercept	0.7591 (0.0069), <0.0001	0.7779 (0.0097), <0.0001	0.7646 (0.007), <0.0001	0.7723 (0.007), <0.0001	0.7934 (0.0098), <0.0001	0.7716 (0.007), <0.0001	0.7929 (0.0098), <0.0001
Treatment arm (sunitinib)		-0.0379 (0.0138), 0.0059			-0.0422 (0.0139), 0.0024		-0.0427 (0.014), 0.0023
Progression Status (Progression)			-0.0342 (0.006), <0.0001			0.0064 (0.008), 0.4276	0.001 (0.0104), 0.9237
Treatment Status (Off treatment)				-0.0625 (0.0054), <0.0001	-0.0747 (0.008), <0.0001	-0.0514 (0.0074), <0.0001	-0.0562 (0.0112), <0.0001
Treatment Arm*Progression Status							0.0114 (0.0164), 0.4892
Treatment Arm*Treatment Status					0.0224 (0.0108), 0.0378		0.0085 (0.0149), 0.5661
Progression Status*Treatment Status						-0.0281 (0.0125), 0.0246	-0.0367 (0.0176), 0.0370
Treatment Arm*Progression Status*Treatment Status							0.0161 (0.0253), 0.5238

	Estimate (SE), p-value						
Parameters/Fit statistics	Model 1: intercept only	Model 2: add Treatment Arm	Model 3: add Progression Status	Model 4: add Treatment Status	Model 5: add Treatment Arm to Model 4	Model 6: add Progression Status to Model 4	Model 7: add Progression Status to Model 5
-2 Log Likelihood	-5225.7	-5233.2	-5258.2	-5359.6	-5371.3	-5364.9	-5378.2
AIC (smaller is better)	-5219.7	-5225.2	-5250.2	-5351.6	-5359.3	-5352.9	-5358.2
BIC (smaller is better)	-5205.5	-5206.3	-5231.3	-5332.6	-5330.9	-5324.5	-5310.9
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EQ-5D-3L, EQ-5D 3-level questionnaire; SE, standard error.							

Results suggest there are significant negative consequences for patient utility associated with treatment discontinuation. That patient utility suffers with treatment discontinuation is consistent with expectations. Though disease progression was not estimated to be an independent predictor of patient utility in the best-fitting model, disease progression and treatment discontinuation are correlated in the data, and the parameter estimate for treatment status is likely capturing some of the effect of disease progression upon patient utility.

Randomisation to sunitinib is found to be a significant negative predictor of utility in Table 28, even when controlling for the interaction between treatment arm and treatment status. This is consistent with the findings from CheckMate 025, in which randomisation to nivolumab was associated with better patient EQ-5D-3L utility than randomisation to everolimus.[59] In CheckMate 214, as in CheckMate 025, this treatment arm effect tallies with the higher response rates in the intervention arm (ORR 41.6% versus 26.5%, NIVO+IPI versus sunitinib; Table 9, Section B.2.6).

Table 29 summarises the CheckMate 214 EQ-5D-3L utility estimates applicable to the model health states (to three decimal places), calculated using the Model 5 data in Table 28, alongside the TA417 model health state utility estimates for nivolumab and everolimus from similar analyses of CheckMate 025 EQ-5D-3L utility data. The interaction parameter in Model 5 implies that randomisation to sunitinib continues to have a slight negative effect upon utility even after discontinuation. A similar result was found in CheckMate 025, whereby a post-progression utility benefit was implied for nivolumab versus everolimus patients, as shown in Table 29. This consistent finding is explained by the potential for immunotherapeutic benefit to sustain beyond immunotherapy discontinuation, and beyond RECIST-defined disease progression.

Comparing the EQ-5D-3L data from CheckMate 214 with those from CheckMate 025, the direction and size of parameter estimates illustrate consistency across two contemporary trials with similar treatment protocols and study conditions. The data in Table 29 show utility levels across the two studies to be very similar, implying that utility for previously treated, advanced RCC patients receiving second-line treatment is, *ceteris paribus*, similar to utility for previously untreated, intermediate- or poor-risk advanced RCC patients receiving first-line treatment.

Table 29: Economic model health state values implied by CheckMate 214 EQ-5D-3L data, and health state values used in TA417 based on CheckMate 025 EQ-5D-3L data

Economic model health states	**CheckMate 214 – Intermediate-/poor-risk patients EQ-5D-3L utility**	
	NIVO+IPI	**Sunitinib**
PFS On Tx, PPS On Tx	0.793	0.751
PFS Off Tx, PPS Off Tx	0.719	0.699
TA417 Economic model health states	**CheckMate 025 – ITT EQ-5D-3L utility**	
	Nivolumab	**Everolimus**
PFS On Tx, PFS Off Tx	0.798	0.762
PPS On Tx, PPS Off Tx	0.728	0.697
Key: EQ-5D-3L, EQ-5D 3-Level questionnaire; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.		

B.3.4.2. Health-related quality-of-life studies

A search for published studies reporting HRQL or utility data for previously untreated RCC patients was conducted alongside the search for cost-effectiveness studies, as reported in Appendix G. The study selection methods and results of the HRQL review are shown in Appendix H.

Twenty-five studies were included in the final review[58, 83-106], and the details of these studies are tabulated in Appendix H. The level of reporting and findings varied substantially across studies. Most reported utility results were based on EQ-5D-3L data, though few clearly reported the valuation algorithm used.

Across different studies, patient utility was found to differ by treatment strategy, treatment status and disease status, suggesting the approach to model specification in Section B.3.4.1 is supported by the wider evidence base. Not all studies clearly reported sample sizes, though no study reported a larger sample than the ITT sample in CheckMate 214. The results in Table 29 are, on balance, consistent with the wider literature.

Table 20 of Section B.3.2.2 summarised the sources of utility data in TA169, TA215 and ID591, while utility values used in TA417 are summarised in Table 29. In each previous and ongoing appraisal of previously untreated, advanced RCC, and the only previous appraisal of an immune checkpoint inhibitor in advanced RCC, EQ-5D-3L data from the pivotal clinical effectiveness RCT have informed utility assumptions in the economic analysis. These within-RCT data arguably provide the greatest contribution to the wider understanding of patient HRQL of the body of work identified in Appendix G, and the findings from CheckMate 214 patients presented in Section B.3.4.1 can help to improve this understanding.

B.3.4.3. Adverse reactions

Patient-reported EQ-5D-3L data are expected to capture the HRQL effects of TRAEs, and as such these data are used to inform all health state utility assumptions in the analysis base case (Section B.3.4.4); no further utility adjustments are made to account for AEs in the base case analysis. This approach is consistent with the committee-preferred analysis in TA417.

Nevertheless, for thoroughness, additional utility decrements for drug-related Grade 3 or 4 AEs are considered in a scenario in Section B.3.8.3. Table 8.15-2 of the CheckMate 214 CSR reports drug-related AEs for intermediate-/poor-risk subjects, for those AEs experienced by at least 15% of patients in either treatment arm, and reports Grade 3/4 events within these.[33] The HRQL impact of each of these Grade 3/4 TRAEs is considered, and the numbers of events are shown in Table 30. The AE profiles of NIVO+IPI and sunitinib are clearly different, in line with expectations. Table 30 illustrates a higher incidence of Grade 3–4 lipase increase, pruritus and rash for NIVO+IPI patients, but a higher incidence of Grade 3–4 anaemia, asthenia, diarrhoea, fatigue, mucosal inflammation, palmar-plantar erythrodysesthesia syndrome, stomatitis, thrombocytopenia, vomiting and, in particular, hypertension for sunitinib patients.

Table 30: Drug-related Grade 3–4 AEs for intermediate-/poor-risk patients in CheckMate 214, for those AEs experienced by at least 15% of patients in either treatment arm

AE description	Number of Grade 3–4 AEs	
	NIVO+IPI (N=423)	Sunitinib (N=416)
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Palmar-plantar erythrodysesthesia syndrome	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Key: AE, adverse event; NIVO+IPI, nivolumab + ipilimumab.
Source: CheckMate 214 CSR, Table 8.15-2

To capture the HRQL impact of these AEs in an economic scenario analysis, the Table 30 incidence data were first used to estimate weekly incidence probabilities using median TTD data (Section B.3.3.4) to inform estimated exposure period assumptions on each treatment arm. Estimated disutility associated with each Grade 3–4 AE was sourced from previous and ongoing NICE TAs in advanced RCC; these data are shown in Table 31. AE disutility is assumed to last for the duration of the AE; Table 32 shows AE duration data from CheckMate 214 and summarises the assumptions involved in assigning a duration estimate to each AE considered. Finally, the data across Table 30, Table 31 and Table 32 were used to calculate weekly AE QALY decrements associated with treatment exposure in each arm of CheckMate 214. The total AE weekly QALY decrements associated with NIVO+IPI

and sunitinib exposure were by this method estimated to be -0.00014 and -0.00040 QALYs, respectively. As shown in Section B.3.8.3, the base case analysis assumption that patient utility implications of these AEs are captured by EQ-5D-3L data introduces slight bias against NIVO+IPI if this assumption is inaccurate.

Table 31: Utility decrement estimates for Grade 3–4 AEs

Grade 3–4 AE	Disutility	Data source
Anaemia	-0.081	Utility decrement for anaemia Grade 3+ from TA215 Manufacturer submission (pazopanib for 1L RCC)[107]
Asthenia	-0.204	Assumed equal to decreased fatigue
Diarrhoea	-0.261	Disutility for diarrhoea Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Decreased appetite	-0.038	Disutility for decreased weight Grade 3+ from ID1029 MS, which used decreased appetite as a proxy (lenvatinib with everolimus for previously treated RCC)[108]
Dysgeusia	-0.038	Assumed equal to decreased appetite
Fatigue	-0.204	Disutility for fatigue Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Hypertension	-0.153	Disutility for hypertension Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Hypothyroidism	-0.204	Assumed equal to asthenia
Lipase increased	-0.081	Assumed equal to anaemia
Mucosal inflammation	-0.040	Assumed equal to stomatitis
Nausea	-0.255	Disutility for nausea Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Palmar-plantar erythrodysesthesia syndrome	-0.040	Assumed equal to stomatitis
Pruritus	-0.040	Assumed equal to stomatitis
Rash	-0.040	Assumed equal to stomatitis
Stomatitis	-0.040	Disutility for stomatitis Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Thrombocytopenia	-0.081	Assumed equal to anaemia
Vomiting	-0.030	Disutility for vomiting Grade 3+ from ID1029 MS (lenvatinib with everolimus for previously treated RCC)[108]
Key: AE, adverse event, RCC, renal cell carcinoma; TA, Technology Appraisal.		

Table 32: Duration of Grade 3–4 AEs in CheckMate 214, All Patient data

Grade 3–4 AE	Median duration (weeks)		Assumption and data source
	NIVO+IPI	Sunitinib	
Anaemia	4.86	3.14	Assumed to be Hepatic (CM214 CSR 8.7.3-2)[33]
Asthenia	4.86	3.14	Assumed to be Hepatic (CM214 CSR 8.7.3-2)[33]
Diarrhoea	2.14	3.42	Assumed to be Gastrointestinal (CM214 CSR 8.7.2-2)[33]
Decreased appetite	2.14	3.42	Assumed to be Gastrointestinal (CM214 CSR 8.7.2-2)[33]
Dysgeusia	2.14	3.42	Assumed to be Gastrointestinal (CM214 CSR 8.7.2-2)[33]
Fatigue	15.43	15.43	Assumed to be Endocrine (CM214 CSR 8.7.1-2)[33]*
Hypertension	4.86	3.14	Assumed to be Hepatic (CM214 CSR 8.7.3-2)[33]
Hypothyroidism	15.43	15.43	Assumed to be Endocrine (CM214 CSR 8.7.1-2)[33]*
Lipase increased	4.86	3.14	Assumed to be Hepatic (CM214 CSR 8.7.3-2)[33]
Mucosal inflammation	9.00	15.00	Assumed to be Skin (CM214 CSR 8.7.6-2)[33]
Nausea	2.14	3.42	Assumed to be Gastrointestinal (CM214 CSR 8.7.2-2)[33]
Palmar-plantar erythrodysesthesia syndrome	9.00	15.00	Assumed to be Skin (CM214 CSR 8.7.6-2)[33]
Pruritus	9.00	15.00	Assumed to be Skin (CM214 CSR 8.7.6-2)[33]
Rash	9.00	15.00	Assumed to be Skin (CM214 CSR 8.7.6-2)[33]
Stomatitis	9.00	15.00	Assumed to be Skin (CM214 CSR 8.7.6-2)[33]
Thrombocytopenia	4.86	3.14	Assumed to be Hepatic (CM214 CSR 8.7.3-2)[33]
Vomiting	2.14	3.42	Assumed to be Gastrointestinal (CM214 CSR 8.7.2-2)[33]

Key: AE, adverse event; CM, CheckMate; CSR, Clinical Study Report; NIVO+IPI, nivolumab + ipilimumab.
Notes: * Equal to median duration of immune-modulating medication; data for sunitinib unavailable, assumed equal to NIVO+IPI.

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

In line with the NICE reference case[57], the utility values underpinning the cost-effectiveness analysis are based on HRQL measured directly by patients using the EQ-5D-3L questionnaire, valued using public preferences as per the UK time trade-off (TTO) valuation set used in many previous appraisals. Both in line with the reference case and following previous appraisals in RCC, the key EQ-5D-3L data were collected within the pivotal RCT for this submission.

Table 33 summarises the utility values used in the cost-effectiveness analysis. The treatment-arm-, treatment-status- and progression-status-defined utility values in Table 33 are based on the data in Table 29. "*PFS On 1L Tx*", "*PFS Off 1L Tx*", "*PPS On 1L Tx*" and "*PPS Off 1L Tx*" values are the utility values estimated from the best-fitting mixed model analysis of CheckMate 214 data, reported in Table 29 and described throughout Section B.3.4.1. The "*PPS, Off 1L Tx, 2L NIVO*" and "*PPS, Off 1L Tx, 2L TKI/mTOR*" utility values are CheckMate 025 estimates, also shown in Table 29. In accordance with TA417 preferred assumptions, utility for patients who receive second-line axitinib is assumed to be equal to utility for patients who received everolimus in CheckMate 025, and, generally, VEGFR TKI outcomes are assumed equivalent to mammalian target of rapamycin (mTOR) inhibitor outcomes. In alignment with the findings from CheckMate 025 utility analysis, "*PPS, Off 1L Tx, 2L…*" utility values are applied from the point at which first-line treatment has been discontinued and disease has progressed, for the mean time-to-disease-progression in TA417. The "*PPS, Off 1L Tx*" utility value is applied for both the following: patients who have discontinued first-line treatment and whose disease has progressed, but do not go on to receive second-line treatment; and for those patients who do receive second-line treatment, after the time at which their advanced RCC is expected to have progressed for a second time.

As indicated in Table 33, the health state utility values for patients who receive sunitinib as a front-line treatment for advanced RCC are assumed to apply to patients who instead receive another VEGFR TKI (pazopanib). This is a simplifying assumption, but one that is consistent with previous appraisals.[26] Notably, the ERG and Committee in TA417 preferred to assume axitinib (TKI) utility was equivalent to CheckMate 025 everolimus (mTOR inhibitor) utility. Scenarios testing this assumption are provided in Section B.3.8.3.

The approach to utility assumptions is a key strength of this appraisal. The analysis uses large-sample, pivotal RCT patient-reported EQ-5D-3L data, examined in a systematic and appropriate manner. With an eye to consistency with NICE decision-making evidence for downstream treatments, we believe this approach meets Institute preferences and provides NICE with the prospect of an objective evidence base with which to address the decision problem at hand.

Table 33: Summary of utility values for cost-effectiveness analysis

State	Utility value	95% CI	Reference in submission	Justification
Patients receiving NIVO+IPI as first-line advanced RCC treatment				
PFS, On 1L Tx	0.793	Variance-covariance matrix used; see Section B.3.6.1	Section B.3.4.1	Estimated directly from systematic analysis of EQ-5D-3L data from patients informing effectiveness estimates, in line with the NICE Reference Case[57]
PFS, Off 1L Tx	0.719			
PPS, On 1L Tx	0.793			
PPS, Off 1L Tx	0.719			
PPS, Off 1L Tx, 2L NIVO*	0.798			
PPS, Off 1L Tx, 2L TKI/mTOR*	0.762			
Patients receiving sunitinib or pazopanib as first-line advanced RCC treatment				
PFS, On 1L Tx	0.751	Variance-covariance matrix used; see Section B.3.6.1	Section B.3.4.1	Estimated directly from systematic analysis of EQ-5D-3L data from patients informing effectiveness estimates, in line with the NICE Reference Case[57]
PFS, Off 1L Tx	0.699			
PPS, On 1L Tx	0.751			
PPS, Off 1L Tx	0.699			
PPS, Off 1L Tx, 2L NIVO*	0.798			
PPS, Off 1L Tx, 2L TKI/mTOR*	0.762			
Grade III/IV AE utility decrements (explored in scenario analysis)				
Anaemia	-0.081	[-0.07,-0.10]		

State	Utility value	95% CI	Reference in submission	Justification
Asthenia	-0.204	[-0.16,-0.24]	Section B.3.4.3	Best available estimates, sourced from previous NICE TAs in RCC
Diarrhoea	-0.261	[-0.21,-0.31]		
Decreased appetite	-0.038	[-0.03,-0.05]		
Dysgeusia	-0.038	[-0.03,-0.05]		
Fatigue	-0.204	[-0.16,-0.24]		
Hypertension	-0.153	[-0.12,-0.18]		
Hypothyroidism	-0.204	[-0.16,-0.24]		
Lipase increased	-0.081	[-0.07,-0.10]		
Mucosal inflammation	-0.040	[-0.03,-0.05]		
Nausea	-0.255	[-0.21,-0.30]		
Palmar-plantar erythrodysesthesia syndrome	-0.040	[-0.03,-0.05]		
Pruritus	-0.040	[-0.03,-0.05]		
Rash	-0.040	[-0.03,-0.05]		
Stomatitis	-0.040	[-0.03,-0.05]		
Thrombocytopenia	-0.081	[-0.07,-0.10]		
Vomiting	-0.030	[-0.02,-0.04]		

Key: 1L, first-line; 2L, second-line; AE, adverse event; CI, confidence interval; EQ-5D-3L, EQ-5D 3-level questionnaire; NIVO, nivolumab; IPI, ipilimumab; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; RCC, renal cell carcinoma; TKI, tyrosine-kinase inhibitor.
Notes: * Applied for mean estimated time to progression on each treatment, from TA417.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Appendix I reports a systematic review of published cost and resource use for previously untreated advanced RCC patients in the UK. Thirteen studies were included in the final review.[58, 86, 93, 96, 98, 101, 102, 109-114] Previous TAs are a key source of information on the NHS resource burden associated with advanced RCC treatment, and this is highlighted by the review. Resource use assumptions described in this section are primarily based on assumptions used in previous NICE TAs in RCC.

B.3.5.1. Intervention and comparators' costs and resource use

Table 34 displays the total drug acquisition cost per cycle (per administration for NIVO+IPI) for the intervention and comparators, using list prices for all treatments, and in line with the dosing regimens described in Section B.2.3

Table 35 shows the administration costs included in the model. Administration for NIVO+IPI has been assumed to be delivered as a regular day/night case, and uses the same NHS Reference Costs code as the only published appraisal of nivolumab and ipilimumab as combination therapy, TA400.[115, 116]

To calculate the number of NIVO+IPI vials required per administration for an average NHS England patient while accounting for wastage, real-world evidence from BMS market research was used. Data on NHS England advanced RCC patients, including patient weight, were collected in 423 patients treated across Addenbrooke's Hospital, Cambridge and The Christie Hospital, Manchester (mean weight 78.27kg, 95% CI 76.61–79.94).[117]

A log-normal distribution of patient weights was estimated based on the moments of patient weight data, and the average number of whole vials required for dosing was calculated. 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, TA384, TA400, TA417).[73, 116, 118, 119]

Patient weight data collected from advanced RCC patients treated in NHS practice in Addenbrooke's Hospital and The Christie are expected to more accurately reflect the patient weights anticipated for this indication in England and Wales. As only summary data were available for these patients, the distribution of patient weights estimated from CheckMate 214 data was adjusted to reflect Christie/Addenbrooke's patients, using the ratio of mean patient weight across Christie/Addenbrooke's and the intermediate-/poor-risk group of CheckMate 214.[33] Scenario analyses are provided using the patient weight data from CheckMate 214 and using the data from Ipsos Global Oncology Monitor, previously used in TA417, in Section B.3.8.3.[73]

BMS interviews with medical oncologists have 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.[54] To explore the implications of vial sharing for model results, a scenario is explored in Section B.3.8.3 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 (78.27kg), divided by vial size (40mg or 100mg).

In respect to adherence, the proportion of planned nivolumab and ipilimumab doses received was calculated from CheckMate 214 intermediate-/poor-risk patient-level data as [redacted] respectively, accounting for the proportion of doses delayed ([redacted], with average dose delay of 15 and 20 days, respectively) and the proportion of doses omitted ([redacted]). To account for the relative dose intensity (RDI) for sunitinib and pazopanib, an RDI of 86% was assumed, consistent with TA169, which used a value quoted by Pfizer from the Phase III trial for sunitinib in previously untreated patients[43], and TA215, which used patient-level data from the pazopanib Phase III VEG105192 study.[120]

As described in Sections B.3.2.3 and B.3.3.4, BMS believe the maximum treatment duration would be 5 years from NIVO+IPI treatment initiation. This assumption is incorporated into the economic analysis base case, as described in Sections B.3.3.4 and B.3.5.1. However, due to the uncertainty around the length of a stopping rule and the relevance to NHS England practice, the impact of relaxing this assumption is tested in a scenario in Section B.3.8.3.

Table 34: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators, list prices

Drug	Cost per vial/pack	Vial size/ Tablets per /pack	Dosing regimen	Vials/ Tablets per admin	Proportion of doses received	Total cost per week*	Source (cost, regimen, RDI)
Nivolumab	£1,097.00	100mg	4x 3mg/kg Q3W IV, then 3mg/kg Q2W IV	1.64	[redacted]	[redacted] for Week 1 to 12 [redacted] for Week 13+	MIMS[121], CM-214 CSR[33], CM-214 CSR[33]
	£439.00	40mg		2.01			
Ipilimumab	£15,000.00	200mg	4x 1mg/kg Q3W IV	0.02	[redacted]	[redacted]	MIMS[122], CM-214 CSR[33], CM-214 CSR[33]
	£3,750.00	50mg		1.98			
Pazopanib	£1,121.00	30x400mg	800mg oral daily	2.00	86%	£449.89	MIMS[123], pazopanib SPC[65], TA215[107]
	£560.50	30x200mg		4.00			
Sunitinib	£3,138.80	28x50mg	50mg oral daily, 4 weeks on, 2 weeks off	1.00	86%	£674.84	MIMS[124], sunitinib SPC[64], TA169[60]
	£1,569.40	28x25mg		2.00			
	£784.70	28x12.5mg		4.00			

Key: CM, CheckMate; CSR, clinical study report; IV, intravenous; MIMS, Monthly Index of Medical Specialities; Q2W, once every 2 weeks; Q3W, once every 3 weeks; RDI, relative dose intensity; SPC, Summary of Product Characteristics; TA, Technology Appraisal.
Note: *, Although costs in the table are provided by week, the model costs nivolumab and ipilimumab by administration, i.e. a single cost applied every 2 or 3 weeks.

Table 35: Administration costs

Administration	Unit cost	Source
Intravenous	£310.00	NHS Reference Costs 2016-2017 Daycase and Reg Day/Night, Deliver more Complex Parenteral Chemotherapy at First Attendance, Currency code SB13Z[125]
Oral	£0.00	Assumption
Key: NHS, National Health Service.		

B.3.5.2. Health-state unit costs and resource use

Base case resource use and unit cost estimates attributed to disease management are shown in Table 36. Resource use assumptions from TA333, subsequently used to inform assumptions in TA417, were assessed and considered the most relevant assumptions to use for this appraisal. These assumptions are also broadly consistent with those used in TA169 and TA215. The TA417 health state resource use assumptions were validated at clinical review, and the resource use type and frequency data in Table 36 reflect the feedback received. NHS costs associated with each resource were sourced from Personal Social Services Research Unit (PSSRU) or NHS Reference Cost documentation and reflect 2016–2017 prices.

Table 36: Resource use and costs associated with model health states

Health State	Resource	Frequency per week	Source	Cost	Source
PFS	GP visit	0.25	TA417	£32.00	PSSRU (2017) Section 10.3b p165, General practitioner - unit costs, Patient contact lasting 9.2 minutes, including direct staff costs, excluding qualifications
	CT scan	0.08	TA417	£142.99	NHS ref costs 2016-17; "Diagnostic imagining, outpatient, CT scan more than 3 areas", RD27Z
	Blood test	0.25	TA417	£3.06	NHS ref costs 2016-17; "Directly assessed pathological services - haematology", DAPS05
Total weekly cost associated with PFS health states					**£20.68**
PPS	GP visit	0.25	TA417	£32.00	PSSRU (2017) Section 10.3b p165, General practitioner - unit costs, Patient contact lasting 9.2 minutes, including direct staff costs, excluding qualifications
	Specialist community nurse visit	0.38	TA417	£67.04	PSSRU (2015) Section 10.4 p172, Nurse specialist (community), 1-hour patient time, excluding qualifications, adjusted for inflation to 2016/2017 prices
	Pain medication	7.00	TA417	£5.46	TA333 Table 44: (BNF section 4.7.2 Opioid analgesics (morphine sulphate 1 mg/mL, net price 50-mL vial = £5.00), adjusted for inflation to 2016/2017 prices
Total weekly cost associated with PPS health states					**£71.38**

Key: BNF, British National Formulary; DAPS, directly assessed pathological services; NHS, National Health Service; PFS, progression-free survival; PPS, post-progression survival; PSSRU, Personal Social Services Research Unit; TA, Technology Appraisal.

B.3.5.3. Adverse reaction unit costs and resource use

The NHS cost implications of TRAEs are considered in the base case analysis. The Grade 3/4 TRAEs described in Sections B.3.4.3 and their estimated costs are shown in Table 37. These costs were sourced by searching previous NICE appraisals in RCC. The appraisal for nivolumab in previously treated, advanced renal cell carcinoma (TA417) was first searched and provided the cost source for anaemia. The appraisal for lenvatinib with everolimus for previously treated, advanced RCC (ID1029) provided the cost sources for asthenia, diarrhoea, decreased appetite, hypertension, nausea, stomatitis and vomiting.

Applying these costs to the cycle probability of each event, calculated from CheckMate 214 data as described in Section B.3.4.3, produces AE cycle costs of £4.24 for patients receiving NIVO+IPI and £15.21 for patients receiving sunitinib.

For simplicity, the cycle cost associated with Grade 3/4 AEs for pazopanib patients is assumed to be equivalent to AE cycle cost for sunitinib patients. Given evidence on the relative safety profiles of pazopanib and sunitinib in RCC patients, this assumption is explored in a scenario in Section B.3.8.3, with pazopanib AE costs being decreased by 10% of the difference between the AE costs for the NIVO+IPI and sunitinib arms.

Table 37: Costs associated with TRAEs

Grade 3/4 adverse event	Cost per episode	Source
Anaemia	£280.03	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref Costs 16-17
Asthenia	£659.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17) + Cost of F2F community nurse + contact of £42 (Source: PSSRU 2017)
Diarrhoea	£788.25	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16) inflated to 2016/17 (PSSRU)
Decreased appetite	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Dysgeusia	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Fatigue	£659.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17) + Cost of F2F community nurse + contact of £42 (Source: PSSRU 2017)
Hypertension	£859.78	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17) + Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (£172.67) (Source NHS Reference costs 2016/17) + 2 follow up GP visits (£35) Source: PSSRU 2017
Hypothyroidism	£659.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17) + Cost of F2F community nurse + contact of £42 (Source: PSSRU 2017)
Lipase increased	£280.03	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref Costs 16-17
Mucosal inflammation	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Nausea	£788.25	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16) inflated to 2016/17 (PSSRU)
Palmar-plantar erythrodysesthesia syndrome	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Pruritus	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Rash	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)

Grade 3/4 adverse event	Cost per episode	Source
Stomatitis	£617.11	Non-elective short stay unit cost of £617.11 (Source: NHS Reference costs 2016/17)
Thrombocytopenia	£280.03	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref Costs 16-17
Vomiting	£788.25	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16) inflated to 2016/17 (PSSRU)
Key: AE, adverse event; CC, complication and comorbidity; F2F, face-to-face; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.		

B.3.5.4. Miscellaneous unit costs and resource use

Subsequent therapy costs

For durable responders to first-line immune checkpoint inhibitor therapy, in tandem with survival plateau expectations, there is anticipation that further systemic therapy will not be warranted. For many patients who discontinue first-line treatment, however, further lines of systemic therapy are available and are likely to be used within NHS England centres, as outlined in Section B.1.3. For economic analysis, the different subsequent treatment cost implications of first-line treatment selection are important. At second-line, those patients who have previously received sunitinib or pazopanib are likely to receive nivolumab monotherapy, whereas those who receive NIVO+IPI as a first-line treatment will not. Third- and even fourth-line treatment choices may be consequential for economic analysis, but less so, and for simplicity, and in line with the subsequent immune checkpoint inhibitor treatment survival implications set out in Section B.3.3.2, the subsequent treatment cost implications considered herein are those incurred at second-line.

In CheckMate 214, at the 7 August 2017 database lock, 47.5% of intermediate-/poor-risk patients on the NIVO+IPI arm, and 59.7% of intermediate-/poor-risk patients on the sunitinib arm had received subsequent cancer therapy [redacted].[33] Table 38 describes the subsequent therapy received by intermediate-/poor-risk patients on each arm of CheckMate 214. Clinical opinion stated that it is likely that all patients failing sunitinib will go on to receive subsequent therapy, whereas in the NIVO+IPI arm, clinician opinion was that approximately 40% of patients would not require subsequent treatment.[46] In the model base case, it is assumed that [redacted].

Table 38: Subsequent therapies received by >5% of intermediate-/poor-risk patients in CheckMate 214

	From	
To	**NIVO+IPI**	**Sunitinib**
Nivolumab	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]

Key: NIVO+IPI, nivolumab + ipilimumab.
Notes: Patients may have received more than one type of subsequent therapy.
Source: CheckMate 214 CSR[33]

However, discussions with NHS clinical oncologists detailed that this subsequent treatment list is not reflective of current UK clinical practice. Expert opinion was that the choices at second-line therapy would be between axitinib, cabozantinib and nivolumab, and for NIVO+IPI-treated patients, re-treatment with nivolumab is not currently an option, based on current guidelines and evidence. There was also the discussion that patients receiving subsequent cabozantinib after sunitinib would experience substantial side effects, and that clinicians may want to give patients a break from VEGFR TKIs.[54] Cabozantinib was also described as a potent but toxic drug, with axitinib used as an additional less toxic option.[46] This was interpreted to mean that 50% of patients receiving subsequent therapy on the NIVO+IPI arm would go on to receive cabozantinib and 50% would receive axitinib, and it is expected that 75% of patients receiving subsequent therapy on the sunitinib arm would receive nivolumab, with the remaining 25% receiving cabozantinib, in keeping with current practice.

Subsequent therapy options are based on this opinion in the base case, detailed in Table 39.

Table 39: Subsequent therapies based on clinical opinion

	From	
To	**NIVO+IPI**	**Sunitinib**
Nivolumab	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Key: NIVO+IPI, nivolumab + ipilimumab.		

The costs of each subsequent treatment per model cycle are detailed in Table 40. In all cases, drug costs have been sourced from Monthly Index of Medical Specialities (MIMS)[121, 123, 124, 126-128], and applied to dosing regimens reflective of each treatment's Summary of Product Characteristics (SPC). [redacted]

[redacted] For nivolumab monotherapy and everolimus, mean TTD was [redacted], and for sunitinib and pazopanib, mean TTD was assumed equal to axitinib TTD [redacted], due to the similar mechanism of action (TKIs).[73] For cabozantinib, in the absence of data on mean TTD, [redacted] was used as a proxy.[129] TTD data and assumptions are presented in Table 41. Subsequent treatment costs are applied as a one-off cost to patients who have newly discontinued treatment and remained alive.

Table 40: Subsequent therapy – drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators

Drug	Cost per vial/pack	Vial size/Tablets per /pack	Dosing regimen	Vials/ Tablets per admin	Proportions of doses received	Total cost per model cycle	Source (cost, regimen, RDI)
Nivolumab	£439.00	40mg	3mg/kg Q2W IV	6.00	[redacted]	[redacted]	MIMS[121], nivolumab SPC[130], [redacted][59]
Sunitinib	£3,138.80	28 x 50mg	50mg daily orally, 4 weeks on, 2 weeks off	1.00	[redacted]	[redacted]	MIMS[124], sunitinib SPC[64], [redacted][131]
Pazopanib	£1,121.00	30 x 400mg	800mg daily orally	2.00	[redacted]	[redacted]	MIMS[123], pazopanib SPC[65], [redacted][107]
Axitinib	£3,517.00	56 x 5mg	5mg BID orally	1.00	[redacted]	[redacted]	MIMS[128], axitinib SPC[132], [redacted][59]
Cabozantinib	£5,143.00	30 x 60mg	60mg daily orally	1.00	[redacted]	[redacted]	MIMS[126], cabozantinib SPC[67], [redacted][129]
Everolimus	£2,673.00	30 x 10mg	10mg daily orally	1.00	[redacted]	[redacted]	MIMS[127], everolimus SPC[133], [redacted][59]

Key: BID, twice daily; IV, intravenous; MIMS, Monthly Index of Medical Specialities; Q2W, once every 2 weeks; RDI, relative dose intensity; SPC, Summary of Product Characteristics; TA, Technology Appraisal.

Table 41: Duration of subsequent therapies

	Average length of subsequent treatment (weeks)	Source
Nivolumab	[redacted]	[redacted]
Sunitinib	[redacted]	
Pazopanib	[redacted]	
Axitinib	[redacted]	
Cabozantinib	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Key: TA, Technology Appraisal.		

End-of-life costs

The cost of care immediately prior to death is taken from a King's Fund report into improving choice at end of life[134], and is the average cost of community and acute care for patients with cancer in the last 8 weeks of their life reported by the authors, inflated to 2016/2017 levels.[135]

The cost for 8 weeks of care is £6,353.01. This is assumed to be spread evenly across the last 8 weeks of a patient's life and is applied as a cost of £794.13 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 is not a key driver of results, as over 99% of patients die within the model time horizon in the base case analysis. Nevertheless, to test the sensitivity of the results to this input, data from an alternative source was considered. The mean estimated cost of end-of-life health and social care in patients in England and Wales across various cancers, inflated to 2016/17 prices, is estimated to be £6,273.94 using data from a different study,[136] serving to validate the estimate from King's Fund data.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base case analysis inputs

Table 42 presents a summary of the variables included in the model, their base case values and the measurement of uncertainty and distribution.

Table 42: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Drug costs			
Nivolumab drug costs (100mg formulation)	[redacted]	Not included in SA	Section B.3.5.1
Nivolumab drug costs (40mg formulation)	[redacted]	Not included in SA	
Ipilimumab drug costs (200mg formulation)	[redacted]	Not included in SA	
Ipilimumab drug costs (50mg formulation)	[redacted]	Not included in SA	
Pazopanib drug costs	£449.89	Not included in SA	
Sunitinib drug costs	£674.84	Not included in SA	
Proportion of doses of nivolumab received	[redacted]	[redacted]	
Proportion of doses of ipilimumab treatment received	[redacted]	[redacted]	
Proportion of doses of sunitinib received	86.00%	Triangular (0.72,1)	
Proportion of doses of pazopanib received	86.00%	Triangular (0.72,1)	
Proportion of doses of subsequent nivolumab received	[redacted]	[redacted]	Section B.3.5.4
Proportion of doses of subsequent sunitinib received	[redacted]	[redacted]	
Proportion of doses of subsequent pazopanib received	[redacted]	[redacted]	
Proportion of doses of subsequent axitinib received	[redacted]	[redacted]	
Proportion of doses of subsequent cabozantinib received	[redacted]	[redacted]	
Proportion of doses of subsequent everolimus received	[redacted]	[redacted]	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Admin and health state costs			
One-off progression costs	£0.00	Not included in SA	Section B.3.5.2
End of life costs	£6,353.01	Gamma (5169.06,7657.21)	
GP visit cost	£32.00	Gamma (26.04,38.57)	
Community Nurse Visit Cost	£67.04	Gamma (54.55,80.8)	
CT Scan cost	£142.99	Gamma (116.34,172.35)	
Blood Test cost	£3.06	Gamma (2.49,3.69)	
Consultant visit cost	£219.19	Gamma (178.34,264.19)	
Disease management analgesic costs	£5.46	Gamma (4.44,6.58)	
Nivolumab administration cost - first visit	£310.00	Gamma (252.23,373.63)	Section B.3.5.1
Nivolumab administration cost - subsequent visits	£310.00	Gamma (252.23,373.63)	
Ipilimumab administration cost	£0.00	Gamma (0,0)	
Sunitinib administration cost	£0.00	Gamma (0,0)	
Pazopanib administration cost	£0.00	Gamma (0,0)	
Adverse event costs			
Cost of treating adverse event Anaemia	£280.03	Gamma (227.84,337.52)	Section B.3.5.3
Cost of treating adverse event Asthenia	£659.11	Gamma (536.28,794.42)	
Cost of treating adverse event Diarrhoea	£788.25	Gamma (641.35,950.07)	
Cost of treating adverse event Decreased appetite	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Dysgeusia	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Fatigue	£659.11	Gamma (536.28,794.42)	
Cost of treating adverse event Hypertension	£859.78	Gamma (699.55,1036.28)	
Cost of treating adverse event Hypothyroidism	£659.11	Gamma (536.28,794.42)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Cost of treating adverse event Lipase increased	£280.03	Gamma (227.84,337.52)	
Cost of treating adverse event Mucosal inflammation	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Nausea	£788.25	Gamma (641.35,950.07)	
Cost of treating adverse event Palmar-plantar erythrodysesthesia syndrome	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Pruritus	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Rash	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Stomatitis	£617.11	Gamma (502.11,743.8)	
Cost of treating adverse event Thrombocytopenia	£280.03	Gamma (227.84,337.52)	
Cost of treating adverse event Vomiting	£788.25	Gamma (641.35,950.07)	
Resource use			
GP visits per week, PFS	0.25	Gamma (0.2,0.3)	Section B.3.5.2
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)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Average length of subsequent nivolumab TOT (weeks)	[redacted]	[redacted]	Section B.3.5.4
Average length of subsequent sunitinib TOT (weeks)	[redacted]	[redacted]	
Average length of subsequent pazopanib TOT (weeks)	[redacted]	[redacted]	
Average length of subsequent axitinib TOT (weeks)	[redacted]	[redacted]	
Average length of subsequent cabozantinib TOT (weeks)	[redacted]	[redacted]	
Average length of subsequent everolimus TOT (weeks)	[redacted]	[redacted]	
Average length of subsequent nivolumab PFS (weeks)	[redacted]	[redacted]	
Average length of subsequent everolimus PFS (weeks)	[redacted]	[redacted]	
Average length of subsequent axitinib PFS (weeks)	[redacted]	[redacted]	
Proportion of nivolumab+ipilimumab patients receiving subsequent therapy	[redacted]	[redacted]	Section B.3.5.4
Proportion of sunitinib patients receiving subsequent therapy	[redacted]	[redacted]	
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Nivolumab	0.00	Dirichlet (PSA only)	
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Sunitinib	0.00	Dirichlet (PSA only)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Pazopanib	0.00	Dirichlet (PSA only)	
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Axitinib	0.30	Dirichlet (PSA only)	
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Cabozantinib	0.30	Dirichlet (PSA only)	
Proportion of patients from Nivolumab+ipilimumab receiving subsequent Everolimus	0.00	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Nivolumab	0.60	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Sunitinib	0.00	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Pazopanib	0.00	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Axitinib	0.00	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Cabozantinib	0.20	Dirichlet (PSA only)	
Proportion of patients from Sunitinib receiving subsequent Everolimus	0.00	Dirichlet (PSA only)	
Proportion of patients from Pazopanib receiving subsequent Nivolumab	0.60	Dirichlet (PSA only)	
Proportion of patients from Pazopanib receiving subsequent Sunitinib	0.00	Dirichlet (PSA only)	
Proportion of patients from Pazopanib receiving subsequent Pazopanib	0.00	Dirichlet (PSA only)	

<table>
<tr><th>Variable</th><th>Value</th><th>Measurement of uncertainty and distribution: CI (distribution)</th><th>Reference</th></tr>
<tr><td>Proportion of patients from Pazopanib receiving subsequent Axitinib</td><td>0.00</td><td>Dirichlet (PSA only)</td><td rowspan="3"></td></tr>
<tr><td>Proportion of patients from Pazopanib receiving subsequent Cabozantinib</td><td>0.20</td><td>Dirichlet (PSA only)</td></tr>
<tr><td>Proportion of patients from Pazopanib receiving subsequent Everolimus</td><td>0.00</td><td>Dirichlet (PSA only)</td></tr>
<tr><td colspan="4">Health state utilities</td></tr>
<tr><td>CM214 Mixed model parameter, Constant</td><td>0.79</td><td rowspan="4">Multivariate normal<table><tr><td></td><td>Constant</td><td>Off tx</td><td>Sunitinib</td><td>Int; off tx & sunitinib</td></tr><tr><td>Constant</td><td>9.58E-05</td><td>-1.32E-05</td><td>-9.58E-05</td><td>1.32E-05</td></tr><tr><td>Off tx</td><td>-1.32E-05</td><td>6.34E-05</td><td>1.32E-05</td><td>-6.34E-05</td></tr><tr><td>Sunitinib</td><td>-9.58E-05</td><td>1.32E-05</td><td>1.94E-04</td><td>-2.47E-05</td></tr><tr><td>Int; off tx & sunitinib</td><td>1.32E-05</td><td>-6.34E-05</td><td>-2.47E-05</td><td>1.17E-04</td></tr></table></td><td rowspan="4">Section B.3.4.1</td></tr>
<tr><td>CM214 Mixed model parameter, Decrement - assigned to off treatment</td><td>-0.07</td></tr>
<tr><td>CM214 Mixed model parameter, Decrement - assigned to sunitinib</td><td>-0.04</td></tr>
<tr><td>CM214 Mixed model parameter, Decrement – interaction; off treatment and sunitinib</td><td>0.02</td></tr>
<tr><td>CM025 Mixed model parameter, Constant</td><td>0.80</td><td rowspan="4">Multivariate normal<table><tr><td></td><td>Constant</td><td>Comparator</td><td>Progressed</td><td>Int comp & PD</td></tr><tr><td>Constant</td><td>1.09E-04</td><td>-1.10E-04</td><td>-2.00E-05</td><td>2.00E-05</td></tr><tr><td>Comparator</td><td>-1.10E-04</td><td>2.25E-04</td><td>2.00E-05</td><td>-4.00E-05</td></tr><tr><td>Progressed</td><td>-2.00E-05</td><td>2.00E-05</td><td>5.40E-05</td><td>-5.00E-05</td></tr><tr><td>Int comp & PD</td><td>2.00E-05</td><td>-4.00E-05</td><td>-5.00E-05</td><td>1.03E-04</td></tr></table></td><td rowspan="4">Section B.3.4.4</td></tr>
<tr><td>CM025 Mixed model parameter, Decrement - assigned to the comparator arm</td><td>-0.04</td></tr>
<tr><td>CM025 Mixed model parameter, Decrement - disease progression</td><td>-0.07</td></tr>
<tr><td>CM025 Mixed model parameter, Decrement – interaction; disease progression and assigned to the comparator arm</td><td>0.00</td></tr>
<tr><td colspan="4">Adverse event disutilities</td></tr>
<tr><td>Utility decrement for adverse event Anaemia</td><td>-0.08</td><td>Normal (-0.07,-0.1)</td><td rowspan="2">Section B.3.4.3</td></tr>
<tr><td>Utility decrement for adverse event Asthenia</td><td>-0.20</td><td>Normal (-0.16,-0.24)</td></tr>
</table>

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Utility decrement for adverse event Diarrhoea	-0.26	Normal (-0.21,-0.31)	
Utility decrement for adverse event Decreased appetite	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Dysgeusia	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Fatigue	-0.20	Normal (-0.16,-0.24)	
Utility decrement for adverse event Hypertension	-0.15	Normal (-0.12,-0.18)	
Utility decrement for adverse event Hypothyroidism	-0.20	Normal (-0.16,-0.24)	
Utility decrement for adverse event Lipase increased	-0.08	Normal (-0.07,-0.1)	
Utility decrement for adverse event Mucosal inflammation	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Nausea	-0.26	Normal (-0.21,-0.3)	
Utility decrement for adverse event Palmar-plantar erythrodysesthesia syndrome	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Pruritus	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Rash	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Stomatitis	-0.04	Normal (-0.03,-0.05)	
Utility decrement for adverse event Thrombocytopenia	-0.08	Normal (-0.07,-0.1)	
Utility decrement for adverse event Vomiting	-0.03	Normal (-0.02,-0.04)	
Adverse event probabilities			
Cycle probability for nivolumab+ipilimumab of adverse event Anaemia	0.00	Beta (0,0)	Section B.3.5.3

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Cycle probability for nivolumab+ipilimumab of adverse event Asthenia	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Diarrhoea	0.00	Beta (0,0.01)	
Cycle probability for nivolumab+ipilimumab of adverse event Decreased appetite	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Dysgeusia	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Fatigue	0.00	Beta (0,0.01)	
Cycle probability for nivolumab+ipilimumab of adverse event Hypertension	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Hypothyroidism	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Lipase increased	0.00	Beta (0,0.01)	
Cycle probability for nivolumab+ipilimumab of adverse event Mucosal inflammation	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Nausea	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Palmar-plantar erythrodysesthesia syndrome	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Pruritus	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Rash	0.00	Beta (0,0)	
Cycle probability for nivolumab+ipilimumab of adverse event Stomatitis	0.00	Beta (0,0)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Cycle probability for nivolumab+ipilimumab of adverse event Thrombocytopenia	0.00	Beta (0,0)	
Cycle probability for sunitinib of adverse event Anaemia	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Asthenia	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Diarrhoea	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Decreased appetite	0.00	Beta (0,0)	
Cycle probability for sunitinib of adverse event Dysgeusia	0.00	Beta (0,0)	
Cycle probability for sunitinib of adverse event Fatigue	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Hypertension	0.01	Beta (0,0.02)	
Cycle probability for sunitinib of adverse event Hypothyroidism	0.00	Beta (0,0)	
Cycle probability for sunitinib of adverse event Lipase increased	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Mucosal inflammation	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Nausea	0.00	Beta (0,0)	
Cycle probability for sunitinib of adverse event Palmar-plantar erythrodysesthesia syndrome	0.00	Beta (0,0.01)	
Cycle probability for sunitinib of adverse event Pruritus	0.00	Beta (0,0)	

<table>
<tr><th>Variable</th><th>Value</th><th>Measurement of uncertainty and distribution: CI (distribution)</th><th>Reference</th></tr>
<tr><td>Cycle probability for sunitinib of adverse event Rash</td><td>0.00</td><td>Beta (0,0)</td><td rowspan="3"></td></tr>
<tr><td>Cycle probability for sunitinib of adverse event Stomatitis</td><td>0.00</td><td>Beta (0,0.01)</td></tr>
<tr><td>Cycle probability for sunitinib of adverse event Thrombocytopenia</td><td>0.00</td><td>Beta (0,0.01)</td></tr>
<tr><td colspan="4">Survival Parameters – PFS</td></tr>
<tr><td>PFS Independent Spline 2 knots - hazard - gamma 1 γ0(nivolumab+ipilimumab)</td><td>-4.22</td><td rowspan="4">Multivariate normal<table><tr><td>gamma 0</td><td>0.104</td><td>-0.138</td><td>-0.032</td><td>0.023</td></tr><tr><td>gamma 1</td><td>-0.138</td><td>0.233</td><td>0.065</td><td>-0.052</td></tr><tr><td>gamma 2</td><td>-0.032</td><td>0.065</td><td>0.022</td><td>-0.019</td></tr><tr><td>gamma 3</td><td>0.023</td><td>-0.052</td><td>-0.019</td><td>0.017</td></tr></table></td><td rowspan="7">Section B.3.3.3</td></tr>
<tr><td>PFS Independent Spline 2 knots - hazard - gamma 1 γ1(nivolumab+ipilimumab)</td><td>3.30</td></tr>
<tr><td>PFS Independent Spline 2 knots - hazard - gamma 1 γ2(nivolumab+ipilimumab)</td><td>0.46</td></tr>
<tr><td>PFS Independent Spline 2 knots - hazard - gamma 1 γ3(nivolumab+ipilimumab)</td><td>-0.24</td></tr>
<tr><td>PFS Independent Spline 1 knot - hazard - gamma 1 γ0 (sunitinib)</td><td>-3.58</td><td rowspan="3">Multivariate normal<table><tr><td>gamma 0</td><td>0.050</td><td>-0.059</td><td>-0.003</td></tr><tr><td>gamma 1</td><td>-0.059</td><td>0.102</td><td>0.006</td></tr><tr><td>gamma 2</td><td>-0.003</td><td>0.006</td><td>0.000</td></tr></table></td></tr>
<tr><td>PFS Independent Spline 1 knot - hazard - gamma 1 γ1 (sunitinib)</td><td>2.91</td></tr>
<tr><td>PFS Independent Spline 1 knot - hazard - gamma 1 γ2 (sunitinib)</td><td>0.13</td></tr>
<tr><td colspan="4">Survival Parameters – TTD</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td rowspan="2">Multivariate normal<table><tr><td>shape</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>rate</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td rowspan="3">Section B.3.3.4</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>1.03</td><td rowspan="2">Multivariate normal<table><tr><td>shape</td><td>0.004</td><td>0.005</td></tr><tr><td>rate</td><td>0.005</td><td>0.008</td></tr></table></td></tr>
<tr><td>[redacted]</td><td>0.10</td></tr>
</table>

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference
Pazopanib TTD hazard ratio versus sunitinib	0.95	Log-normal (0.78,1.15)	Section B.3.3.4
Survival Parameters – OS			
OS Independent Log-logistic shape(nivolumab+ipilimumab)	1.17	Multivariate normal scale 0.006 -0.005 shape -0.005 0.011	Section B.3.3.1
OS Independent Log-logistic scale(nivolumab+ipilimumab)	41.76		
OS Independent Log-logistic shape (sunitinib)	1.33	Multivariate normal scale 0.004 -0.002 shape -0.002 0.006	
OS Independent Log-logistic scale (sunitinib)	25.24		
Immunotherapeutic effect parameters			
Probability of immunotherapy effect occurring	0.50	Beta (0.4,0.6)	Section B.3.3.2
Proportion of first-line patients receiving immunotherapy effect	0.30	Normal (0.24,0.36)	
Proportion of second-line patients receiving immunotherapy effect	0.18	Normal (0.15,0.22)	

Key: CI, confidence interval; CM214, CheckMate 214; HR, hazard ratio; int, interaction; ITT, intent-to-treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PPS, post-progression survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SA, sensitivity analysis; TOT, time on treatment; TTD, time to treatment discontinuation; tx, treatment.

[redacted]

B.3.6.2. Assumptions

The assumptions of the economic analysis are described in Table 43. The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of data, assumptions are designed to minimise potential bias in the analysis. These two statements are illustrated by the likely direction of bias and justification for analysis assumptions, summarised in Table 43.

Table 43: Summary of assumptions of the economic analysis

#	Assumption	Likely direction of bias	Justification
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs.	No bias expected	Sections A.10, B.3.2.2
2	Lifetime OS for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with NIVO+IPI is captured by a log-logistic model fit to OS KM data from intermediate- or poor-risk patients in the intervention arm of CheckMate 214, subject to an immune-response survival benefit for a minority of patients treated with NIVO+IPI, as described in #4.	No bias expected	Sections A.10, B.3.2.2 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
3	Lifetime OS for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with sunitinib is captured by a log-logistic model fit to OS KM data from intermediate- or poor-risk patients in the comparator arm of CheckMate 214, subject to an immune-response survival benefit for a minority of patients treated with nivolumab as a second-line treatment, as described in #4.	No bias expected	Sections A.10, B.3.3.1 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
4	Those patients who achieve a durable response to NIVO+IPI or nivolumab monotherapy are anticipated to have a 50% probability of receiving benefit from an immunotherapeutic survival effect and have death risk equivalent to age-matched general population data from this point.	No bias expected	Sections A.10, B.3.3.2 Inference of NHS Clinical Oncologist expert data to inform KM data extrapolation is in line with NICE DSU TSD 14 guidance[69]

#	Assumption	Likely direction of bias	Justification
5	Lifetime PFS for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with NIVO+IPI is captured by a spline 2-knots hazard model fit to PFS KM data from intermediate- or poor-risk patients in the intervention arm of CheckMate 214, subject to assumption #7.	No bias expected	Sections A.10, B.3.3.3 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
6	Lifetime PFS for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with sunitinib is captured by a spline 1-knots hazard model fit to PFS KM data from intermediate- or poor-risk patients in the intervention arm of CheckMate 214, subject to assumption #7.	No bias expected	Sections A.10, B.3.3.3 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
7	Post-progression survival on any model arm and in any model cycle is determined by the area between extrapolated PFS and extrapolated OS, unless PFS>OS, in which case PPS is assumed to be zero and PFS is assumed to be equal to extrapolated OS.	No bias expected	Sections A.10, B.3.3.3 This is a consequence of the partitioned survival approach to modelling, as recognised in NICE DSU TSD 19.[137] It is not expected to introduce directional bias in this application.
8	Pazopanib OS and PFS are assumed to be equal to sunitinib OS and PFS.	No bias expected	Sections A.10, B.2.9, B.3.3.1- B.3.3.3 Head-to-head trial evidence, ITC results incorporating this evidence and wider network evidence, alongside clinical opinion, are supportive of these assumptions in advanced RCC patients unstratified by risk.

#	Assumption	Likely direction of bias	Justification
9	NIVO+IPI treatment duration for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with NIVO+IPI is captured [redacted] to TTD KM data from intermediate- or poor-risk patients in the intervention arm of CheckMate 214.	No bias expected	Sections A.10, B.3.3.4 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
10	In order to reduce NHS and patient burden, treatment with NIVO+IPI will not exceed 5 years.	No bias expected	Section B.3.3.4
11	Sunitinib treatment duration for NHS England patients with previously untreated advanced RCC with intermediate- or poor-risk who are treated with sunitinib is captured [redacted] to TTD KM data from intermediate- or poor-risk patients in the intervention arm of CheckMate 214.	No bias expected	Sections A.10, B.3.3.4 NICE DSU TSD 14 guidance[69] is followed to apply survival analysis to incomplete outcome data, and select the most plausible parametric model for the base case analysis.
12	The ratio between median pazopanib TTD and median sunitinib TTD is assumed to represent a HR to estimate pazopanib TTD from assumed sunitinib TTD in this economic analysis.	No bias expected	Section B.3.3.4 In the absence of more accurate TTD data for pazopanib patients, these data are used as the best available to inform a necessary assumption for treatment duration.
13	[redacted] of patients who withdraw from first-line treatment NIVO+IPI treatment and [redacted] of patients who withdraw from first-line sunitinib treatment are assumed to go on to subsequent systemic treatment.	No bias expected	Section B.3.5.4 Those patients who have a durable response to NIVO+IPI have the potential for an immune checkpoint inhibitor quality of life and survival benefit without the need for further toxic systemic treatment; by contrast, all patients who withdraw from sunitinib treatment who are fit enough for subsequent active treatment are expected to receive further treatment.

#	Assumption	Likely direction of bias	Justification
14	50% of patients who receive NIVO+IPI first-line and go on to receive second-line treatment are assumed to receive cabozantinib as second-line treatment and the remainder are assumed to receive the less toxic available treatment, axitinib; 75% of patients who receive sunitinib or pazopanib first-line and go on to receive second-line treatment are assumed to receive nivolumab monotherapy and the remainder are assumed to receive cabozantinib.	No bias expected	Section B.3.5.4 NHS Clinical Oncologist-informed estimates of subsequent treatment distribution are considered to be the most valid source of data available, given the immaturity of CheckMate 214 data and the evolving NHS England subsequent treatment landscape.
15	HRQL for NHS England patients with previously untreated advanced RCC treated with NIVO+IPI or sunitinib is affected by treatment status and type of active treatment, and captured by the mixed model analysis of EQ-5D-3L data from CheckMate 214 patients with a stepwise approach to variable selection, while the HRQL effects of subsequent second-line treatment are captured by mixed model analysis of EQ-5D-3L data from CheckMate 025 with a stepwise approach to variable selection.	No bias expected	Section B.3.4.5 Utility data estimated directly from systematic analysis of EQ-5D-3L data from a large sample of trial patients who also inform effectiveness estimates is the gold standard source of utility assumptions, following the NICE Reference Case[57]
16	HRQL for NHS England patients with previously untreated advanced RCC treated with pazopanib is assumed to be no different to HRQL for patients treated with sunitinib.	Against pazopanib	Section B.3.4.5 A simplifying assumption used in the absence of head-to-head utility data versus pazopanib. As the expected bias is against a comparator, the assumption is tested in a scenario in Section 5.8.3

#	Assumption	Likely direction of bias	Justification
17	HRQL effects of NIVO+IPI and sunitinib TRAEs are captured by patient EQ-5D-3L questionnaires.	Against NIVO+IPI	Sections B.3.4.4, B.3.4.5 The weekly on-treatment AE cost and utility consequences of sunitinib treatment were greater than those for NIVO+IPI treatment in intermediate-/poor-risk patients, from incidence data on most frequent AEs, duration of exposure data and duration of AE estimates.
18	AE cost and utility implications of pazopanib treatment are assumed equal to those estimated for sunitinib patients.	Against pazopanib	Sections B.3.4.4, B.3.4.5 A simplifying assumption used in the absence of head-to-head utility data versus pazopanib. As the expected bias is against a comparator, the assumption is tested in a scenario in Section 5.8.3.
19	NHS staff are assumed to meet diligent practices to minimise spending on active treatment acquisition. Cost savings from TKI dose reductions are captured by assuming the smallest applicable pack size is dispensed at each visit. Based on this assumption, CheckMate 214 data, and assumptions in TA169 and TA215 are used to inform assumed % of doses received and paid for by NHS England.	No bias expected	Section B.3.5.1 Consistency with previous appraisals and the analysis perspective on costs.
20	NHS RCC patient weight data collected in Addenbrooke's Hospital and Christie Hospital are assumed to provide the best mean estimate of patient weight for those NHS RCC patients who will benefit from NIVO+IPI if recommended.	No bias expected	Section B.3.5.1 NHS England sourced data considered preferable for this application.

#	Assumption	Likely direction of bias	Justification
21	NIVO+IPI and NIVO without IPI administration cost is assumed to be captured by NHS Reference Cost code SB13Z: Complex Parenteral Chemotherapy – 1st attendance, in a Daycase and Reg Day/Night setting.	No bias expected	Section B.3.5.1 Consistent with assumption informing NICE TA400
22	Disease management costs are assumed to be dependent upon disease status (progressed versus progression-free) and comprise medical practitioner contact, scans and pain medication.	No bias expected	Section B.3.5.1 Consistent with previous NICE TAs in RCC and NHS Oncologist opinion

Key: AE, adverse event; EQ-5D-3L, EQ-5D 3-level questionnaire; HRQL, health-related quality of life; ITC, indirect treatment comparison; KM, Kaplan–Meier; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PFs, progression-free survival; PPS, post-progression survival; PSS, Personal Social Services; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

Table 44 displays base case cost-effectiveness results, in terms of pairwise comparisons between NIVO+IPI and its comparators. Table 45 shows the full incremental cost-effectiveness analysis for NIVO+IPI, sunitinib, pazopanib and cabozantinib. Results are presented applying confidential patient access scheme (PAS) discounts of [redacted] to the list price for nivolumab and [redacted] to the list price for ipilimumab. The complex PAS for sunitinib costs (first cycle is free) is applied in the patient flow sheet, and the complex PAS for pazopanib (costed at the same price as sunitinib) has been applied to the list price of pazopanib, with an additional 12.5% discount applied to each unit.[138, 139] Confidential discounts are available for axitinib, cabozantinib and everolimus. The results shown below assume no commercial price discounts for these drugs.

NIVO+IPI is estimated to offer a high per-patient incremental health benefit, providing nearly twice as many life years (LYs) and time-preference discounted QALYs than sunitinib (8.04 LYs and 4.43 QALYs for NIVO+IPI versus 4.53 LYs and 2.68 QALYs for sunitinib). The estimated incremental cost-effectiveness ratio (ICER) for NIVO+IPI versus sunitinib is £28,068 per QALY gained. Pazopanib provided 4.52 LYs and 2.68 QALYs, with an ICER for NIVO+IPI versus pazopanib of £28,022. Absolute outcomes for pazopanib are similar to sunitinib, due to both arms using the same model inputs for efficacy and utility, with equal treatment acquisition and administration costs. As such, total cost and outcomes are extremely similar across sunitinib and pazopanib model arms. Marginal increases in costs due to the longer TTD for pazopanib patients are not offset by the increase in utility for this health state, and thus the ICER for NIVO+IPI versus pazopanib is slightly lower than versus sunitinib. Pazopanib also provides slightly less expected LYs due to more patients staying on first-line treatment, and less patients being eligible for subsequent therapy at each cycle; this means less pazopanib patients receive the anticipated long-term immunotherapy effect provided by subsequent nivolumab monotherapy than sunitinib patients.

Estimates of clinical outcomes compared with trial results and disaggregated results are presented in Appendix J.

Table 44: Base case pairwise incremental cost-effectiveness results – with patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, NIVO+IPI versus comparator			ICER (NIVO+IPI vs.)
				Costs	Life Years	QALYs	
NIVO+IPI	[redacted]	8.04	4.43				
Sunitinib	[redacted]	4.53	2.68	£49,105.64	3.51	1.75	£28,068.31
Pazopanib	[redacted]	4.52	2.68	£49,029.22	3.51	1.75	£28,021.92
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab + ipilimumab; QALY, quality-adjusted life year.							

Table 45: Base case fully incremental cost-effectiveness results – with patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Sunitinib	[redacted]	4.53	2.68					
Pazopanib	[redacted]	4.52	2.68	£76.42	-0.01	0.00	-£451,411.88	Strictly dominated
NIVO+IPI	[redacted]	8.04	4.43	£49,105.64	3.51	1.75	£28,068.31	£28,068.31
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab + ipilimumab; QALY, quality-adjusted life year.								

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

In the incremental probabilistic analysis, pazopanib is extendedly dominated, whereas it is strictly dominated in the deterministic base case. [redacted]. This QALY gain in the pazopanib arm outweighs the increase in LYs provided by more second-line nivolumab use in the sunitinib arm, in PSA, meaning pazopanib is only extendedly dominated.

Figure 33: PSA scatterplot, NIVO+IPI versus sunitinib

Key: ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab + ipilimumab; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 34: PSA scatterplot, NIVO+IPI versus pazopanib

Key: ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab + ipilimumab; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 35: Cost-effectiveness acceptability curve

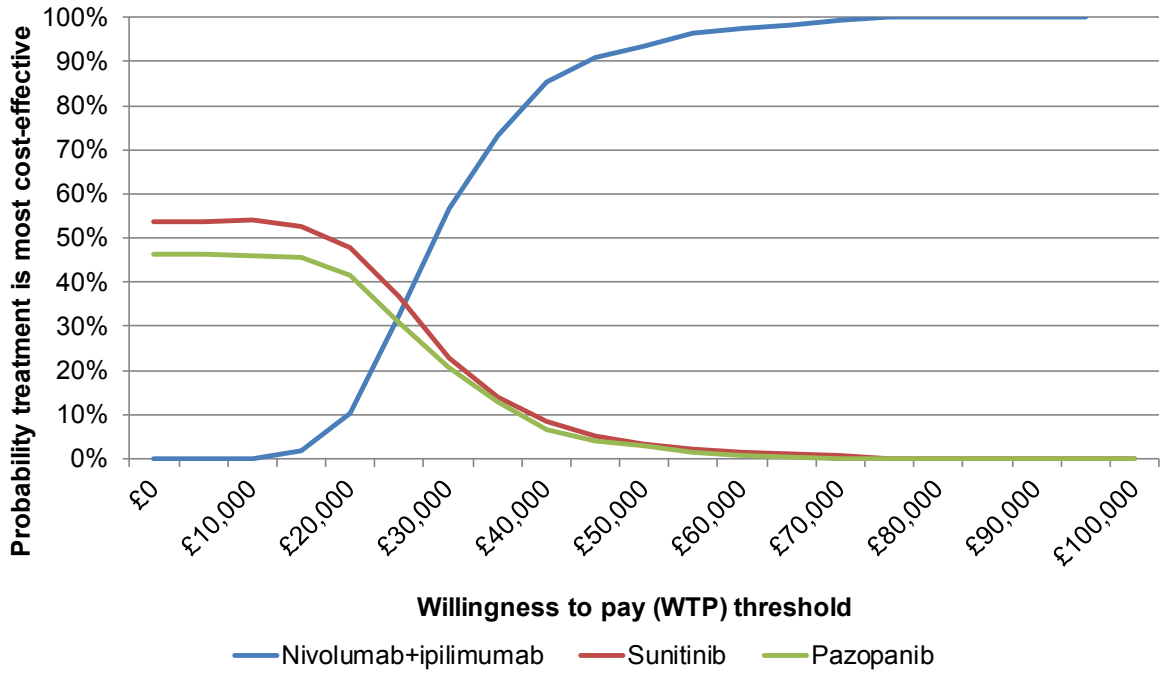


Table 46: Mean probabilistic base case results, pairwise analysis, with PAS

	Total costs	Total life years	Total QALYs	Incremental, NIVO+IPI versus comparator			ICER
				Costs	Life years	QALYs	
NIVO+IPI	[redacted]	8.04	4.43				
Sunitinib	[redacted]	4.53	2.68	£53,248.58	3.50	1.75	£30,405.36
Pazopanib	[redacted]	4.53	2.68	£53,039.70	3.51	1.75	£30,299.82

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab + ipilimumab; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 47: Mean probabilistic base case results, fully incremental analysis, with PAS

	Total costs	Total life years	Total QALYs	Incremental			ICER versus baseline (£/QALY)	ICERs (full incremental analysis)
				Costs	Life years	QALYs		
Sunitinib	[redacted]	4.53	2.68					
Pazopanib	[redacted]	4.53	2.68	£208.88	-0.01	0.00	£263,114.77	Extendedly dominated
NIVO+IPI	[redacted]	8.04	4.43	£53,039.70	3.51	1.75	£30,405.36	£30,405.36

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab + ipilimumab; PAS< patient access scheme; QALY, quality-adjusted life year.

B.3.8.2. Deterministic sensitivity analysis

Figure 36 and Figure 37 show the tornado diagrams depicting the 10 parameters that have the greatest influence on the ICER versus NIVO+IPI in one-way sensitivity analyses (OWSA), when their values were set to their upper and lower 95% CI values.

Estimated pairwise ICERs for NIVO+IPI versus (i) sunitinib and (ii) pazopanib are shown to be reasonably robust to isolated parameter changes. Parameters for the NIVO+IPI TTD curve have the greatest impact on results, with parameters regarding subsequent therapy, immunotherapy effect and the proportion of doses of first-line drugs received, also having an effect, although with a maximum total difference of £5,000.

Figure 36: Tornado diagram showing OWSA results, NIVO+IPI versus sunitinib

Key: CM214, CheckMate 214; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; OWSA, one-way sensitivity analysis; TOT, time on treatment; TTD, time to treatment discontinuation.

Figure 37: Tornado diagram showing OWSA results, NIVO+IPI versus pazopanib

Key: CM214, CheckMate 214; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TOT, time on treatment; TTD, time to treatment discontinuation.

B.3.8.3. Scenario analysis

Table 48 shows results from scenario analyses varying key assumptions in the base case comparisons to sunitinib and pazopanib. Results are robust to changes in the majority of parameters, with changes to discount rate, IO effect, subsequent therapy and overall survival causing the biggest impact on the ICER.

Table 48: Scenario analy1sis

Parameter	Base case	Scenario analysis	Justification	NIVO+IPI vs sunitinib ICER	NIVO+IPI vs pazopanib ICER
Base case				**£28,068**	**£28,022**
Discount rate (costs and utilities)	3.5%	6%	Testing model result sensitivity to discount rate	£33,671	£33,644
Discount rate (costs and utilities)	3.5%	0%		£20,884	£20,827
Time horizon (years)	40	25	Testing model result sensitivity to length of time horizon	£29,553	£29,509
Time horizon (years)	40	30		£28,471	£28,426
Time horizon (years)	40	35		£28,132	£28,086
OS curve choice (curve fit NIVO+IPI and sunitinib)	Log-logistic	Log-normal	Testing the best fitting curve according to AIC	£25,727	£25,680
OS curve choice (dependence)	Independent	Dependent, Log-logistic	Uncertainty in PH assumption	£32,739	£32,685
PFS curve choice (curve fit NIVO+IPI and sunitinib)	Spline 2 knots - hazard - gamma 1, Spline 1 knot - hazard - gamma 1	Spline 1 knot - odds - gamma 1	Testing the same curve with good fit according to AIC/BIC for both NIVO+IPI and sunitinib	£26,972	£26,927
PFS curve choice (dependence)	Independent	Dependent, Spline 1 knot - hazard - gamma 1	Uncertainty in PH assumption	£28,290	£28,244
TTD fitted curve choice (NIVO+IPI and sunitinib)	[redacted]	[redacted]	[redacted]	£30,593	£30,561
TTD proportional hazards assumption/treatment covariate dependence of fitted curves	Independent	[redacted]	Testing model result sensitivity to PH assumption	£28,074	£28,028

Parameter	Base case	Scenario analysis	Justification	NIVO+IPI vs sunitinib ICER	NIVO+IPI vs pazopanib ICER
Base case				**£28,068**	**£28,022**
Vial sharing for nivolumab and ipilimumab	No	Yes	Clinical opinion stated that vial sharing may be feasible in centres that treat large numbers of RCC or malignant melanoma patients	£24,956	£24,906
Probability of durable responders on NIVO+IPI/nivolumab receiving long-term immunotherapy survival benefit	50.0%	0%	Testing model sensitivity to the assumption of long-term immunotherapeutic benefit of first-line NIVO+IPI and second-line nivolumab	£33,392	£33,381
	50.0%	100%		£24,749	£24,690
Average patient weight	BMS RWD	Ipsos UK estimate	Testing alternative sources for patient weights including clinical trial patient data	£25,737	£25,691
		214 Western European patients		£27,831	£27,818
Dosing method	Weight-based	Hybrid dosing (240 Q2W)	Due to the potential change in posology variation submitted to EMA for nivolumab dosing, NIVO+IPI patients are assumed to receive weight-based dosing for the first 12 weeks, followed by either 240mg nivolumab q2w or 480mg nivolumab q4w.	£27,591	£27,545
		Hybrid dosing (480 Q4W)		£25,597	£25,551
		Flat dosing (240 Q2W)	NIVO+IPI patients are assumed to receive either 240mg nivolumab q2w or 480mg nivolumab q4w.	£29,306	£29,259
		Flat dosing (480 Q4W)		£26,987	£26,941

Parameter	Base case	Scenario analysis	Justification	NIVO+IPI vs sunitinib ICER	NIVO+IPI vs pazopanib ICER
Base case				**£28,068**	**£28,022**
Subsequent therapy inputs	Clinician opinion	Re-weighted CheckMate 214 for NICE recommendations	Using clinician trial data for subsequent therapy inputs, restricting use to those therapies approved by NICE	£28,502	£28,501
Proportion of patients receiving subsequent therapy	[redacted]	100%	Testing result sensitivity to alternative subsequent therapy proportions	£30,881	£30,887
		0%		£33,113	£32,822
Pre-progression utility and adverse event treatment cost of patients on pazopanib	Equal to sunitinib	Equal to sunitinib plus/minus 10% of the difference between sunitinib and NIVO+IPI patients for pre-progression utility and adverse event cost, respectively	Patients are believed to prefer pazopanib over sunitinib, and pazopanib has a safer toxicity profile than sunitinib, which would be reflected in HRQL	£28,068	£28,109
Adverse event disutilities applied from the literature	No	Yes	If utility analysis from trial data does not capture the utility impact of adverse events, disutilities from the literature and previous appraisals may reflect the impact of adverse events more accurately	£27,938	£27,878
Alternative end of life cost source	Kings Fund	Round et al.	Round et al. provides an alternative method of estimating end of life care costs	£28,072	£28,025

Parameter	Base case	Scenario analysis	Justification	NIVO+IPI vs sunitinib ICER	NIVO+IPI vs pazopanib ICER
Base case				**£28,068**	**£28,022**
Treatment stopping rule	Yes, 5 years	Yes, 3 years	Testing model sensitivity to NIVO+IPI treatment duration	£24,772	£24,726
		No		£29,658	£29,611

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BMS, Bristol-Myers Squibb; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival; PH, proportional hazards; q2w, every 2 weeks; q4w, every 4 weeks; RCC, renal cell carcinoma; RWD, real-world data; TTD, time to treatment discontinuation.

B.3.8.4. Summary of sensitivity analyses results

Sensitivity and scenario analysis results showed results to be robust to uncertainty around most input parameters. Survival assumptions, however, and those that affect expected treatment acquisition cost (first-line and subsequent), are clearly important for cost-effectiveness results. Parametric modelling of clinical outcomes from CheckMate 214 data was based on NICE DSU TSD 14, and assumptions have been validated at clinical review. While there is uncertainty around the cost-effectiveness of NIVO+IPI in intermediate-/poor-risk patients, care has been taken to inform uncertain assumptions with the best data available, and to be transparent in illustrating the uncertainty around results.

B.3.9. Subgroup analysis

The economic appraisal focusses on the primary endpoint population of intermediate-/poor-risk advanced RCC patients in CheckMate 214, as described in Section B.3.2.1. Section B.2.7 presents relative effectiveness results for CheckMate 214 intermediate-/poor-risk patients, stratified by PD-L1 tumour expression (≥1% versus <1%), an exploratory endpoint in CheckMate 214.

B.3.10. Validation

B.3.10.1. Validation of 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 B.3.2.

As discussed in Section B.3.3.2, meetings with oncologists treating NHS patients with advanced RCC have been key in informing necessary assumptions and validating approaches taken. This process began in early 2016 in preparation for TA417, and, with the oncologists who have guided us, we have aimed to be transparent throughout. Notable help has come from Dr James Larkin, Consultant Medical Oncologist at Royal Marsden NHS Foundation Trust, and Professor John Wagstaff, Deputy Clinical Director at the South West Wales Cancer Research Institute, Swansea, whose informed guidance we are grateful for. As described in

Section B.3.3, notes from each meeting we have drawn upon are disclosed as part of this submission.

The cost-effectiveness model itself 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 subject to review against a checklist of known modelling errors and questioning of the assumptions.

B.3.11. Interpretation and conclusions of economic evidence

As described in Section B.3.10, the methods and data used to analyse the cost effectiveness of NIVO+IPI for previously untreated, advanced RCC patients with intermediate-/poor-risk have been validated and are believed to be the best available. The main weakness of the evaluation is the immaturity of the key clinical outcomes data, which are not sufficient to demonstrate an immune-response OS tail, expected both by the clinical community based on mechanism of action and from the evidence for nivolumab and ipilimumab (used separately and in combination) in trial settings and in clinical practice in advanced RCC patients and melanoma patients.

Cost-effectiveness analysis results are most sensitive to uncertainties around parameter values and other assumptions associated with long-term survival and treatment continuation assumptions. Such sensitivities are inherent to evaluations of immunotherapy technologies, where the potential patient benefit of treatment is great and stands to emerge in full in the future, but the requirement to evaluate and fund treatment is more immediate. An open and transparent approach to model design, description and execution is intended to allow the ERG and Committee to explore and test these uncertainties, in the context of the necessary appraisal of this and other emerging immunotherapy strategies.

While the key OS data are immature for the purposes of HTA, the evidence from CheckMate 214 is a key strength of this economic appraisal. The co-primary endpoints of OS, PFS and ORR are directly relevant to NICE appraisal of health benefits, and the necessary assessment of incremental benefit required to justify incremental cost. That the CheckMate 214 comparator represents routine care for NHS patients is another notable strength for decision-making. The collection of

patient-reported EQ-5D-3L within CheckMate 214 is a third. In many HTA decisions, when the clinical evidence necessarily falls short of these standards, understanding the incremental health benefit of innovative treatment is a far greater challenge. Here, the quality and relevance of clinical evidence to support economic appraisal is strong.

Section B.2.13 highlighted long-term evidence suggesting life expectancy for intermediate- and poor-risk RCC patients is less than two years.[53] Evidence from CheckMate 214, CheckMate 025 and other supportive trials incorporated into this economic analysis suggest survival prospects have improved, with nivolumab as a second-line therapy being the only treatment for advanced RCC patients to have demonstrated a long-term survival benefit before the immune checkpoint inhibitor combination of NIVO+IPI considered herein.

In conclusion, economic analysis based on CheckMate 214 data (and necessary and most plausible assumptions), suggests that even without consideration of the higher weight afforded to end-of-life therapies, NIVO+IPI is both clinically effective and cost-effective as a treatment option for the NHS, for previously untreated, advanced RCC patients with intermediate- or poor-risk.

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B.5. Appendices

Appendix C: Draft summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Health-related quality of life tools

Appendix M: CheckMate 016

Appendix N: CheckMate 214: Secondary outcomes

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Single technology appraisal

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

Dear Suzanne and David,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have looked at the submission received on 5 February 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 **5pm** on 8 March. Your response and any supporting documents should be uploaded to NICE Docs https://appraisals.nice.org.uk/request/45476

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 raised in this letter, please contact Thomas Strong, Technical Lead (thomas.strong@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

CheckMate 214 trial

A1. **Priority question.** For the primary definition of progression-free survival (PFS), patients who received subsequent therapy pre-progression were censored, and patients who received subsequent therapy who had no documented progression were censored (company submission, page 24):

a) Please clarify the justification for censoring for subsequent therapy. If the subsequent therapies received are representative of subsequent therapies that would be received in clinical practice, then there is no need to censor for subsequent therapy in the calculation of PFS.

b) Please provide the total number of patients who were censored due to receiving subsequent therapy in each arm of the trial. Please provide data for (i) intermediate-risk group patients and (ii) poor-risk group patients.

c) Please provide a breakdown of the subsequent therapies received by all patients who were censored for subsequent therapy, for each arm of the trial. Please provide data for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A2. **Priority question.** On page 18 of the company submission, it is stated that patients could continue treatment beyond initial Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. Please clarify, how many (i) intermediate-risk group patients and (ii) poor-risk group patients were treated beyond RECIST-defined progression in each arm of the CheckMate 214 trial.

A3. On page 26 of the company submission, it is stated that "The overall alpha for this study's primary endpoints is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS with at least 80% power and 0.04 to evaluate OS with 90% power, accounting for two formal interim analyses to assess efficacy".

a) Since only 0.001 alpha was allocated for the analysis of objective response rate (ORR), please explain why the result for the difference in independent radiology review committee (IRRC)-assessed ORR on page 32 is quoted with a 95% confidence interval.

b) PFS and ORR were analysed using both investigator-assessed and IRRC-assessed data and PFS was analysed using 2 definitions. Were

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these approaches taken into consideration in the splitting of alpha for the study so that the overall experiment-wise Type 1 error rate remained at 0.05?

c) Were the secondary outcomes i.e. overall survival (OS), PFS and ORR in all randomised patients, taken into consideration in the splitting of alpha for the study, so that the overall experiment-wise Type 1 error rate remained at 0.05?

A4. In Table 7 of the company submission, for the calculation of required sample size, it is stated that "For PFS, 583 events were required among the randomised intermediate/poor risk patients for a two-sided experiment-wise α=0.01 log-rank test, to show a statistically significant difference in PFS between the treatment arms with at least 90% power". However, also in Table 7, it is confirmed that the primary analysis of PFS was conducted when it was expected to observe approximately 465 PFS events. Please clarify why the primary analysis of PFS was planned for when the required number of events had not occurred?

A5. Please explain how the point estimate for the difference in IRRC-assessed ORR and corresponding 95% confidence intervals (company submission, Table 9) were calculated.

A6. On page 29 of the company submission, it is stated that: "After a median follow-up of 25.2 months, deaths had occurred in 140 patients (32.9%) in the NIVO+IPI group and 188 patients (44.5%) in the sunitinib group. Median OS was not reached (NR) (95% confidence interval [CI]: 28.2, not evaluable [NE]) in the NIVO+IPI group and was 26.0 months (95% CI: 22.1, NE) in the sunitinib group". Please clarify how median OS was calculated for the sunitinib arm when only 44.5% of patients had died at the time of analysis.

A7. On page 31 of the company submission, and in the clinical study report, for PFS (primary definition) by investigator assessment, it is stated that "median PFS (primary definition) was 8.2 months for NIVO+IPI and 8.3 months for sunitinib, with a HR of 0.82." The reported hazard ratio (HR) is the same as the HR reported for IRRC-assessed PFS (primary definition), but the median PFS value for NIVO+IPI patients is substantially shorter for investigator-assessed PFS than for IRRC-assessed PFS. It seems unlikely that an identical HR would be reported when the difference between median PFS values is so different between the IRRC and investigator-assessed results. Furthermore, it seems unlikely that the HR would favour NIVO+IPI when median PFS is observed to be longer for sunitinib than for NIVO+IPI. Please clarify, are these results correct?

A8. Please provide the number of events and median OS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

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A9. For the primary definition of IRRC-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A10. For the secondary definition of IRRC-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A11. For the primary definition of investigator-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A12. For the secondary definition of investigator-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A13. Table 9 of the company submission reports the IRCC-assessed ORR findings for intermediate-/poor-risk patients. Please provide the equivalent data for each arm of the trial for (i) intermediate-risk group patients and (ii) poor-risk group patients.

A14. A breakdown of subsequent treatment received on disease progression is presented for all patients in the CheckMate 214 trial in Table 13 of the company submission. Please provide a similar table for (i) intermediate-risk group patients and (ii) poor-risk group patients in each arm of the CheckMate 214 trial.

A15. Please clarify why the incidence of some adverse events (AEs) in Table 16 of the company submission is different to the incidence of the same AEs in Table 15 of the company submission. Is this because not all immune-mediated AEs in Table 16 are necessarily considered to be treatment-related in Table 15?

Network meta-analysis

A16. **Clarification request sent to the company in advance of this letter (13 February 2018).**

The ERG makes the following observations:

- The NMA is constructed from a very large network of 37 trials, and includes a base-case analysis, 2 sensitivity analyses involving meta-regression and a secondary analysis for each outcome (overall survival [OS] and progression-free survival [PFS]) in order to obtain estimates of efficacy for NIVO+IPI versus pazopanib using various methods. For OS, none of these methods are able to

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derive a hazard ratio in the relevant patient population (patients with intermediate-/poor-risk advanced renal cell carcinoma [RCC]) for NIVO+IPI versus pazopanib.

- Since the CheckMate 214 trial links NIVO+IPI to sunitinib, and the COMPARZ trial links sunitinib to pazopanib, the ERG considers that it would be possible to obtain estimates of efficacy (OS and PFS) for NIVO+IPI versus pazopanib in the relevant patient population from one network involving only the CheckMate 214 (NIVO+IPI versus sunitinib) and COMPARZ (pazopanib versus sunitinib) trials, assuming the necessary data were available.

- The ERG note that the company were able to extract a hazard ratio (with 95% confidence intervals [CI]) for PFS for patients with intermediate-/poor-risk advanced RCC in the COMPARZ trial but were unable to extract a hazard ratio for OS for the same population. The ERG has been unable to identify the source from where the hazard ratio for PFS is derived.

- In addition, the ERG notes that the company refers to report of the COMPARZ trial by Motzer et al 2014 (see Table 11, page 48 of the company's submission). The ERG notes that the OS data presented in the table are updated OS data (HR=0.92; 95% CI: 0.79 to 1.06) as opposed to the data reported by Motzer et al 2013 (hazard ratio=0.91; 95% CI, 0.76 to 1.08). The company have the earlier OS data (Motzer et al 2013) in their NMA.

As a result of the observations above, the ERG has the following queries:

1. For PFS, for patients with intermediate-/poor-risk advanced RCC, from which source was the hazard ratio for pazopanib versus sunitinib derived?
2. Did this source not include OS data for the same patient population?
3. If relevant data for OS were not presented in the source from which the HR for PFS was derived, did the company attempt to contact the authors of the COMPARZ trial for the relevant OS data?

Following on from its observations and queries, the ERG makes the following requests:

a. For PFS, please consider conducting a simpler indirect comparison for NIVO+IPI versus pazopanib and NIVO+IPI versus sunitinib using only the data from the CheckMate 214 and COMPARZ trials.
b. For OS, please consider conducting a simpler indirect comparison for NIVO+IPI versus pazopanib and NIVO+IPI versus sunitinib using only the data from the CheckMate 214 and COMPARZ trials if it is possible to obtain a HR for OS for the intermediate-/poor-risk patient population. Please use the most recent OS data where possible.

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A17. **Priority question.** Following the company's response to question A16, the ERG requests that the company performs the following indirect comparisons using data from only the COMPARZ and CheckMate 214 trials.

a) For OS, the ERG requests that the company performs indirect comparisons using data from the letter by Motzer et al. (2014),[1] and the CheckMate 214 trial data in the following patient populations:

   i. poor-risk patient population

   ii. intermediate-risk patient population

   iii. intermediate-/poor-risk patient population (an estimate of HR for this patient population within the COMPARZ trial may be obtained by performing random-effects meta-analysis of the HRs reported for poor-risk and intermediate-risk patient groups separately).

b) For IRRC-assessed PFS, the ERG requests that the company performs 2 indirect comparisons using:

   i. the HR for the intermediate-risk patient population from the supplementary appendix of the COMPARZ trial,[2] and the CheckMate 214 trial data for the intermediate-risk patient population

   ii. the HR for the intermediate-risk patient population from the supplementary appendix of the COMPARZ trial,[2] and the CheckMate 214 trial data for the intermediate-/poor-risk patient population.

Please conduct each of the above indirect comparisons using both the primary and secondary definitions of PFS for the CheckMate 214 trial.

A18. **Priority question.** In the company's initial response to A16, the company states that the HR for pazopanib versus sunitinib for PFS for patients with intermediate risk advanced RCC was derived from Figure S3 of the supplementary appendix of the COMPARZ trial publication, using graph digitising software.

In Appendix D to the company submission (Table 5), the company presents data inputs for the NMA. Here, the HR for pazopanib versus sunitinib favours sunitinib in terms of PFS, whereas in Figure S3 of the supplementary appendix of the COMPARZ trial publication, the HR for pazopanib versus sunitinib clearly favours pazopanib. Please clarify, has the PFS HR for intermediate-risk patients been incorrectly extracted and incorporated in the conducted NMAs? If so, please ensure this error is addressed when performing the ERG requested indirect comparisons.

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Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide in a separate document the Kaplan-Meier analyses listed in a) to h) and to the following specifications:

- Study data set: CheckMate 214 study, August 2017 data cut (or more recent if available).
- Format: please present analysis outputs using the format of the sample table provided at the end of section B (to include censoring times).
- Population: intermediate- and poor-risk population including all patients who were lost to follow-up or withdrawing from the trial.
- Stratification: all Kaplan-Meier analyses to be stratified by treatment and by risk group (intermediate and poor risk).

a) Time to death from any cause (OS) stratified by i) treatment and intermediate risk and ii) treatment and poor risk.

b) Investigator-assessed PFS (primary definition). All patients who received subsequent systemic anti-cancer therapy prior to or without documented progression to be censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

c) Investigator-assessed PFS (secondary definition). All patients who did not progress or die to be censored on the date of the last evaluable tumour assessment, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

d) IRRC-assessed PFS (primary definition). All patients who received subsequent systemic anti-cancer therapy prior to or without documented progression to be censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy, stratified by (i) treatment and intermediate risk and (ii) treatement and poor risk.

e) IRRC-assessed PFS (secondary definition). All patients who did not progress or die to be censored on the date of the last evaluable tumour assessment, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

f) Post-progression survival (PPS) based on investigator-assessed PFS, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

g) PPS based on IRRC-assessed PFS, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

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h) Time to study treatment discontinuation (TTD), stratified by stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

B2. On page 79 of the company submission it states that: "…the log-normal model provided the best statistical fit to each stratified dataset. However, given the immaturity of the OS data and different extrapolation projections of each parametric model, parametric model selection was based primarily on the clinical plausibility of projected OS over the lifetime horizon."

The log-normal model was rejected and the log-logistic model was chosen for OS in the base case based on clinical opinion that 5-year survival would be:

- around 15%-20% for treatment with sunitinib, based on the results of the global expanded-access study reported by Gore et al 2015.[3]
- around 35%-45% for treatment with NIVO+IPI.

Please justify why the log-logistic model for treatment with NIVO+IPI was chosen when each of the 7 independently-fitted models produced 5-year estimates of OS between 33%-44%, and all but the gamma and Weibull models produced estimates of between 35%-44%.

Please also provide further justification as to why the log-logistic model for treatment with sunitinib was chosen when 4 of the 7 independently-fitted models (gamma, exponential, Weibull and Gompertz) produced 5-year estimates of OS between 15%-20%, but the log-logistic model produced a 5-year OS estimate of 24%.

B3. Table 18 in the company submission summarises OS in CheckMate 003, CheckMate 010 and CheckMate 025. Please clarify whether the values reported in Table 18 refer to the ITT population in the 3 studies mentioned or whether they refer to the intermediate-/poor-risk subgroup.

If the values in Table 18 refer to the ITT population, please produce a similar table for the intermediate-/poor-risk subgroup using the most up-to-date data cuts for each trial.

B4. The company models an immunotherapeutic effect on the basis of durable response. On page 32 of the company submission, the company estimates that of 30.1% of patients treated with NIVO+IPI were durable responders in CheckMate 214, based on the proportion of patients who had responded to treatment with NIVO+IPI and were still responding by the time of the August 2017 data cut.

The ERG understands from this that the company links the notion of durable response to ORR and PFS, as ongoing response indicates that no progression event has occurred (except potentially immunotherapy–induced "pseudo progression").

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However, the company appears to model a long-term survival effect for treatment with NIVO+IPI for OS alone. Please clarify how the notion of durable response and long-term survival are linked.

B5. On page 124 of the company submission, it states that "clinician opinion was that approximately 40% of patients would not require subsequent treatment".

In Table 43, assumption 13 it states that" Those patients who have a durable response to NIVO+IPI have the potential for an immune checkpoint inhibitor quality of life and survival benefit without the need for further toxic systemic treatment".

Given that the company models 30% of patients treated with NIVO+IPI to be durable responders who will not require further therapy, please explain why a further [redacted] of patients who are not durable responders are also assumed not to receive further therapy following discontinuation of treatment.

B6. On page 124 of the company submission, it states that "it is assumed that [redacted] of sunitinib patients… receive subsequent therapy.", by which the ERG infers that it is assumed that [redacted] of patients treated with sunitinb do not receive subsequent therapy.

In Table 43, assumption 13, it states that "all patients who withdraw from sunitinib treatment who are fit enough for subsequent active treatment are expected to receive further treatment".

Please confirm whether or not this means that all patients who do not receive subsequent therapy after discontinuing treatment with sunitinib, do not receive it because they are too ill to do so.

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Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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Section C: Textual clarifications and additional points

C1. Please provide the statistical analysis plan (SAP) for CheckMate 214.

C2. In Table 7 of the company submission (page 26), it is stated that "At the time of database lock, the number of deaths was half of the total OS events, so an adjusted alpha of 0.002 was applied (to provide 98% CI)." Should the statement instead be "to provide 99.8% CI"?

C3. In the legend for Table 7 of the company submission, IRRC is defined as "Immune Related Response Criteria". Elsewhere in the submission, IRRC is defined as "independent radiology review committee". Please clarify whether the definition in Table 7 of the company submission is correct.

C4. **Priority question.** We request that you reconsider the information labelled as confidential in your submission and economic model. To ensure that the appraisal process is as transparent as possible, NICE considers it essential that evidence on which the Appraisal Committee's decisions are based is publicly available. With this in mind please could you reconsider the following specific sections:

Data marked 'Academic in Confidence' due to EMA regulatory timelines

NICE does not publish documents prior to positive Committee for Medicinal Products for Human Use (CHMP) approval. Therefore, please consider removing the confidentiality of 'academic in confidence' data which would be lifted at the point of positive EMA regulatory approval.

Cost-effectiveness results marked 'commercial in confidence'

Throughout the submission all components of the cost-effectiveness results are redacted. Please consider reporting transparently the incremental cost-effectiveness ratios (ICERs), as this is key to showing the evidential basis of the committee decision.

Subsequent treatment use assumptions marked 'commercial in confidence'

Throughout the submission you have marked assumptions about the subsequent treatment use, which are informed by clinical opinion, as 'commercial in confidence'. Please consider lifting the confidentiality of these assumptions, as we do not believe that they can be used to back-calculate the confidential discount for nivolumab if the total costs and QALYs are confidential.

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Please resubmit your submission by 5pm Thursday the 8th March and include a revised and fully completed Checklist of Confidential Information stating, for each piece of information, the rationale for treating it as confidential and the expiry date of that confidentiality.

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References

1. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. New Eng J Med. 2014; 370:1769-70.
2. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J*, et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013; 369:722-31.
3. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S*, et al.* Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer. 2015; 113:12.

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Single technology appraisal

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

Dear Elisabeth,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group (ERG), Liverpool Reviews and Implementation Group, and the technical team at NICE. We thank the team for their general comments on the submission and hope that our responses to the individual questions in turn below provide clarity for our approach in the submission and the requested additional information where this has been possible.

We would however like to note that most of the clarification questions received were unexpected, given that they were relating to patient groups not highlighted as of interest in the Final Scope, and thus not highlighted as of interest during the stakeholder consultation phase central to the NICE Single Technology Appraisal process. We have some concerns on the potential threat to the merits of standards for evidence-based decision making if the assessors pursue lines of inquiries for subgroups that were neither predefined in the pivotal RCT nor defined as subgroups of interest in the Institute's Final Scope. While we appreciate the ERG's apparent intentions, we feel the time and resources available to the both the company and the ERG at this review stage are simply not sufficient for appropriately rigorous consideration of fundamental scoping issues and their implications for decision making.

Given the combined (and anticipated licensed) patient population is within the threshold of cost-effectiveness, an analysis by further subgroups appears to us to be redundant. Furthermore, a previous technology appraisal, conducted as part of the review of TA 282, has demonstrated that if a treatment is proven to be cost-effective in a whole population, it would not normally be reasonable to look for subgroups within that population where use was cost ineffective (*point 30 in of Appeal Decision*[1]).

Importantly, the data presented for the overall survival hazard ratios for both groups – presented in Table 7 and Table 9 - indicates no evidence of a difference between the groups and there is a clear *statistically and clinically meaningful* overall survival benefit in both groups; individually and combined. This would further negate the utility of conducting the subgroup analysis for these sub-populations.

There is a small difference in the progression-free survival hazard ratio for the intermediate versus poor risk subgroup (as shown in Table 11 and Table 13) as demonstrated previous PFS does not have a substantial impact on the cost-effectiveness results and in this disease settings, does not provide a great indicator of clinical benefit.

Finally, this subgroup analysis was conducted post-hoc, i.e. not pre-specified as part of the statistical analysis plan and this fact, combined with the small patient numbers in the poor

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risk group (n=91 in the NIVO+IPI arm) would warrant significant caution when considering these subgroups.

Based on the subgroup data provided in this document, a simple cost-effectiveness has been performed. The analyses differs from the company base case only in that they are informed by subgroup-specific overall survival (OS) and time to treatment discontinuation (TTD) CheckMate 214 data. In line with the company base case, log-logistic models were fitted to OS Kaplan-Meier (KM) data for each treatment arm in both subgroups and generalised gamma models were fitted to TTD KM data for each treatment arm. As in the company base case, maximum TTD was set to 5 years. All other assumptions and inputs were kept the same as was done in the submission (Document B, Table 43). Headline results from these analyses, shown in Table 1 and Table 2, indicate minimal differences in incremental cost-effectiveness ratios (ICERs) across the subgroups and in comparison with the company base case analysis (Document B, Table 44: [redacted] per QALY gained versus sunitinib; [redacted] per QALY gained versus pazopanib). Given the similarity of both the clinical data and these cost-effectiveness results to the overall population data and results, BMS believe there is no reason for the ERG to continue analysis of these post-hoc sub-groups.

Table 1: Simple adaptation of company base case cost-effectiveness analysis for the subgroup of CheckMate 214 patients with baseline intermediate risk status

Intermediate risk patients	**Total Costs**	**Total QALYs**	**Total Life Years**	**Incremental, Nivolumab versus comparator**			**ICER (Nivolumab vs.)**
				Costs	**QALYs**	**Life Years**	
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab plus ipilimumab; QALYs, quality adjusted life years.							

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Table 2: Simple adaptation of company base case cost-effectiveness analysis for the subgroup of CheckMate 214 patients with baseline poor risk status

Poor risk patients	**Total Costs**	**Total QALYs**	**Total Life Years**	**Incremental, Nivolumab versus comparator**			**ICER (Nivolumab vs.)**
				Costs	**QALYs**	**Life Years**	
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab plus ipilimumab; QALYs, quality adjusted life years.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed. Accompanying these response letters is also a zipped folder data package, containing the code and supportive data referred to within this response.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

Suzanne Verschuure - Salverda

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Section A: Clarification on effectiveness data

CheckMate 214 trial

A1. **Priority question.** For the primary definition of progression-free survival (PFS), patients who received subsequent therapy pre-progression were censored, and patients who received subsequent therapy who had no documented progression were censored (company submission, page 24):

a) Please clarify the justification for censoring for subsequent therapy. If the subsequent therapies received are representative of subsequent therapies that would be received in clinical practice, then there is no need to censor for subsequent therapy in the calculation of PFS.

The protocol pre-specified PFS - IRRC censoring for subsequent therapy as the primary definition. This ensures that PFS is not confounded by the introduction of subsequent therapy. PFS was also evaluated without censoring for subsequent therapy. Even without censoring for subsequent therapy similar results were observed. Both analyses are provided in the submission document B.

b) Please provide the total number of patients who were censored due to receiving subsequent therapy in each arm of the trial. Please provide data for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data as requested in Table 3 and Table 4 below

Table 3. Intermediate-risk population: number of patients censored for PFS per IRRC (primary definition) due to subsequent anti-cancer therapy

Intermediate risk group	NIVO+IPI (N=334)	Sunitinib (N=332)
Patients censored due to subsequent therapy - n (%)	[redacted]	[redacted]

Key: IRRC, independent radiology review committee; NIVO + IPI, nivolumab plus ipilimumab; PFS, progression-free survival

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Table 4. Poor-risk population: number of patients who were censored for PFS per IRRC (primary definition) due to subsequent anti-cancer therapy

Poor risk group	NIVO + IPI (N=91)	Sunitinib (N=89)
Patients censored due to subsequent therapy - n (%)		

Key: IRRC, independent radiology review committee; NIVO + IPI, nivolumab plus ipilimumab; PFS, progression-free survival.

c) Please provide a breakdown of the subsequent therapies received by all patients who were censored for subsequent therapy, for each arm of the trial. Please provide data for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Table 5 and Table 6 summarises the subsequent anti-cancer therapy (radiotherapy, surgery, or systemic therapy) received by patients who were censored for PFS per IRRC due to subsequent anti-cancer therapy. Patients may be counted more than once in any given anti-cancer therapy category. CSR table S.5.5a summarises the reasons for censoring, counting patients only once by their first occurrence anti-cancer therapy. From CSR table S.5.5a one can match the number of patients censored who received subsequent anti-cancer therapy. However, Table 5 and Table 6 will have more patients compared to CSR table S.5.5a because they are counted in each of the categories and not the first reason for censoring.

Table 5. Intermediate-risk population - Subsequent cancer therapy summary for patients who were censored for PFS per IRRC (primary definition) due to subsequent anti-cancer therapy

	NIVO+IPI (n=334)	Sunitinib (n=333)
Any subsequent therapy, n (%)		
Subsequent radiotherapy, n (%)		
Subsequent surgery, n (%)		
Subsequent systemic therapy, n (%)		
ALK/EGFR tyrosine kinase inhibitors, n (%)		

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	NIVO+IPI (n=334)	Sunitinib (n=333)
Anti-CTLA-4, n (%)		
Ipilimumab		
Anti-PD-1, n (%)		
Nivolumab		
Pembrolizumab		
Anti-PD-L1, n (%)		
Atezolizumab		
Other immunotherapy, n (%)		
IFN		
IFN-α		
IL-2		
Investigational immunotherapy		
Other systemic cancer therapy – chemotherapy, n (%)		
Other systemic cancer therapy – experimental drugs, n (%)		

Key: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; PFS, progression-free survival.

Table 6. Poor-risk population - Subsequent cancer therapy summary for patients who were censored for PFS per IRRC (primary definition) due to subsequent anti-cancer therapy

	NIVO+IPI (n=91)	Sunitinib (n=89)
Any subsequent therapy, n (%)		
Subsequent radiotherapy, n (%)		
Subsequent surgery, n (%)		

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	NIVO+IPI (n=91)	Sunitinib (n=89)
Subsequent systemic therapy, n (%)		
ALK/EGFR tyrosine kinase inhibitors, n (%)		
Anti-CTLA-4, n (%)		
Ipilimumab		
Anti-PD-1, n (%)		
Nivolumab		
Pembrolizumab		
Anti-PD-L1, n (%)		
Other immunotherapy, n (%)		
IFN		
Investigational immunotherapy		
Other systemic cancer therapy – chemotherapy, n (%)		
Other systemic cancer therapy – experimental drugs, n (%)		

Key: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1; PFS, progression-free survival.

A2. **Priority question.** On page 18 of the company submission, it is stated that patients could continue treatment beyond initial Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. Please clarify, how many (i) intermediate-risk group patients and (ii) poor-risk group patients were treated beyond RECIST-defined progression in each arm of the CheckMate 214 trial.

Please find the data requested in Table 7 and Table 8 for intermediate risk and poor risk patients, respectively.

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Table 7. Intermediate-risk population - Patients treated beyond progression

Number of patients (intermediate Risk)	NIVO+IPI (n=334)	Sunitinib (n=333)
Treated beyond progression – N (%)	[redacted]	[redacted]
Key: NIVO+IPI, nivolumab plus ipilimumab.		

Table 8. Poor-risk population - Patients treated beyond progression

Number of patients (poor Risk)	NIVO+IPI (n=90)	Sunitinib (n=87)
Treated beyond progression – N (%)	[redacted]	[redacted]
Key: NIVO+IPI, nivolumab plus ipilimumab.		

A3. On page 26 of the company submission, it is stated that "The overall alpha for this study's primary endpoints is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS with at least 80% power and 0.04 to evaluate OS with 90% power, accounting for two formal interim analyses to assess efficacy".

a) Since only 0.001 alpha was allocated for the analysis of objective response rate (ORR), please explain why the result for the difference in independent radiology review committee (IRRC)-assessed ORR on page 32 is quoted with a 95% confidence interval.

In the CSR, the stratified difference in ORR – IRRC (nivolumab+ipilimumab – sunitinib) was 16.0% (95% CI: 9.8, 22.2), p-value <0.0001. The p-value was less than 0.001, had we adjusted the CIs to 99.9% would have still excluded zero. ORR was added as a primary endpoint for descriptive purposes as requested by the health authority (US driven) for potential accelerated approval.

b) PFS and ORR were analysed using both investigator-assessed and IRRC-assessed data and PFS was analysed using 2 definitions. Were these approaches taken into consideration in the splitting of alpha for the study so that the overall experiment-wise Type 1 error rate remained at 0.05?

This wasn't taken into consideration, the Type 1 error rate was allocated across the three co-primary endpoints: ORR IRRC assessed, censored PFS

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IRRC assessed and OS. Investigator ORR, Investigator PFS and uncensored PFS were secondary/sensitivity analyses.

c) Were the secondary outcomes i.e. overall survival (OS), PFS and ORR in all randomised patients, taken into consideration in the splitting of alpha for the study, so that the overall experiment-wise Type 1 error rate remained at 0.05?

No, as these are secondary outcomes and not primary, the alpha level was controlled through hierarchical testing.

A4. In Table 7 of the company submission, for the calculation of required sample size, it is stated that "For PFS, 583 events were required among the randomised intermediate/poor risk patients for a two-sided experiment-wise α=0.01 log-rank test, to show a statistically significant difference in PFS between the treatment arms with at least 90% power". However, also in Table 7, it is confirmed that the primary analysis of PFS was conducted when it was expected to observe approximately 465 PFS events. Please clarify why the primary analysis of PFS was planned for when the required number of events had not occurred?

In June 2017, the analysis plan was revised to take into account the decreased rate at which the PFS per IRRC assessed events were observed. Revision used 80% power to observe 465 PFS per IRRC events, this was very close to what was actually obtained: N=456 events.

A5. Please explain how the point estimate for the difference in IRRC-assessed ORR and corresponding 95% confidence intervals (company submission, Table 9) were calculated.

The DerSimonian and Laird method was utilised in this study to allow for a stratified analysis of the ORR difference based on the stratification factors collected at randomisation in this study.

A6. On page 29 of the company submission, it is stated that: "After a median follow-up of 25.2 months, deaths had occurred in [redacted] patients ([redacted]%) in the NIVO+IPI group and [redacted] patients ([redacted]%) in the sunitinib group. Median OS was not reached (NR) (95% confidence interval [CI]: 28.2, not evaluable [NE]) in the NIVO+IPI group and was 26.0 months (95% CI: 22.1, NE) in the sunitinib group". Please clarify how median OS was calculated for the sunitinib arm when only [redacted] of patients had died at the time of analysis.

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Proportion sited [redacted] are the number of deaths and does not take into account time to death. Median was computed using Kaplan-Meier methodology that accounts for censoring. The median OS was obtained using cumulative probability and can be extrapolated from Figure 3 on page 3 in the submission document B.

A7. On page 31 of the company submission, and in the clinical study report, for PFS (primary definition) by investigator assessment, it is stated that "median PFS (primary definition) was [redacted] months for NIVO+IPI and [redacted] months for sunitinib, with a HR of [redacted]." The reported hazard ratio (HR) is [redacted] as the HR reported for IRRC-assessed PFS (primary definition), but the median PFS value for NIVO+IPI patients is [redacted] for investigator-assessed PFS than for IRRC-assessed PFS. It seems unlikely that [redacted] would be reported when the difference between median PFS values is [redacted] between the IRRC and investigator-assessed results. Furthermore, it seems unlikely that the HR would [redacted] when median PFS is observed to be [redacted] for sunitinib than for NIVO+IPI. Please clarify, are these results correct?

Results included in the company submission are presented to two digit significance. However, looking at three digits significance HR of [redacted] (**99.1%** CI [redacted]) is observed for PFS (Investigator assessed, primary definition) and PFS (IRRC assessed, primary definition) HR of [redacted] (**99.1%** [redacted]). Hazard ratio is a better measure of the separation between the curves since the hazard ratio is an estimate of the totality of the time frame whereas the median is only a measure at one time point. Delay in treatment effect is observed in both IRRC and investigator assessed versions, however the delay extends further in the investigator assessed version (Figure 1), so that is why the medians are similar. However, later in the investigator assessed PFS plot the separation between arms is clear. In fact, the separation is larger later in time in the investigator assessed version relative to the IRRC version shown by the smaller p-value (0.0166 relative to 0.0331). So overall, despite the similar medians, the treatment effect is (slightly) more pronounced in the investigator assessed version than the IRRC version.

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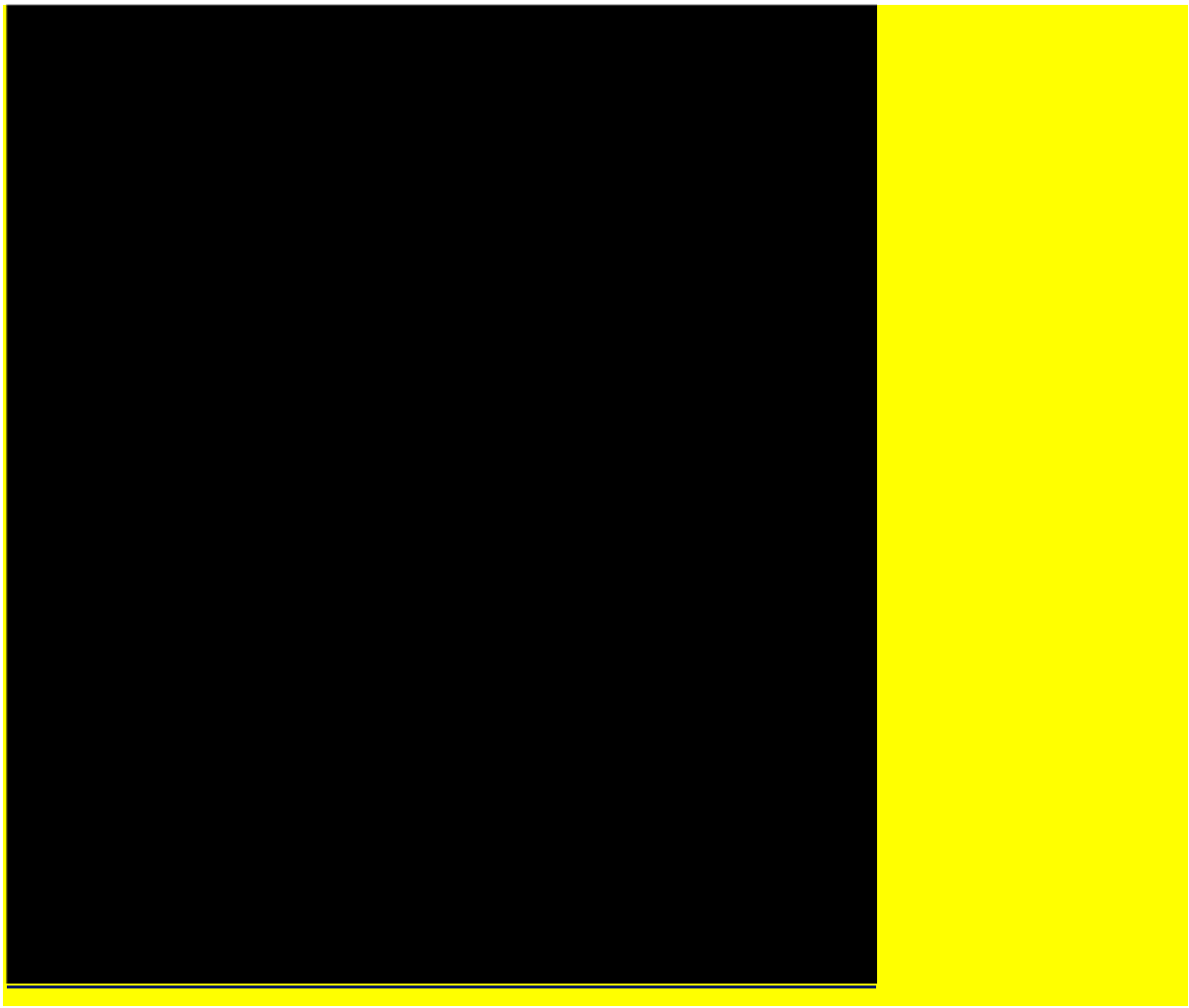
Figure 1. Intermediate-/poor-risk: KM curve of progression free survival based on investigator assessment (primary definition)



A8. Please provide the number of events and median OS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data requested in Table 9 & Table 10 and Table 11 & Table 12 for intermediate risk and poor risk patients, respectively.

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Table 9. Intermediate-risk patients – Median overall survival and hazard ratios

Intermediate Risk	NIVO+IPI (n=334)	Sunitinib (n=333)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	

Key: CI, confidence interval; NE, not evaluable; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival
Notes: [a], NIVO+IPI over Sunitinib

Table 10. Intermediate-risk patients – Overall survival, number at risk

Months											
0	3	6	9	12	15	18	21	24	27	30	33
NIVO+IPI, number at risk											
[redacted]											
Sunitinib, number at risk											
[redacted]											

Key: NIVO+IPI, nivolumab plus ipilimumab.

Table 11. Poor-risk patients – Median overall survival and hazard ratios

Poor risk	NIVO+IPI (n=91)	Sunitinib (n=89)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	

Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival
Notes: [a], NIVO+IPI over Sunitinib

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Table 12. Poor-risk patients – Overall survival, number at risk

Months											
0	3	6	9	12	15	18	21	24	27	30	33
NIVO+IPI, number at risk											
[redacted]											
Sunitinib, number at risk											
[redacted]											
Key: NIVO+IPI, nivolumab + ipilimumab.											

A9. For the primary definition of IRRC-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data requested in Table 13 & Table 14 and Table 15 & Table 16 for intermediate risk and poor risk patients, respectively.

Table 13. Intermediate-risk patients – Progression-free survival based on IRRC – Primary Definition

	NIVO+IPI (n=334)	**Sunitinib (n=333)**
Median OS, months (95% CI)	[redacted]	
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival. **Notes:** [a], NIVO+IPI over Sunitinib		

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Table 14. Intermediate-risk patients - Progression free survival based on IRRC – Primary Definition, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI, number at risk										
[redacted]										
Sunitinib, number at risk										
[redacted]										
Key: IRRC, independent radiology review committee; NIVO+IPI, nivolumab + ipilimumab.										

Table 15. Poor-risk patients – Progression free survival based on IRRC – Primary Definition

	NIVO+IPI (n=91)	**Sunitinib (n=89)**
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival. **Notes:** [a], NIVO+IPI over Sunitinib		

Table 16. Poor-risk patients – Progression Free Survival based on IRRC – Primary Definition, number at risk

Months									
0	3	6	9	12	15	18	21	24	27
NIVO+IPI, number at risk									
[redacted]									
Sunitinib, number at risk									
[redacted]									
Key: IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab.									

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A10. For the secondary definition of IRRC-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data requested in Table 17 & Table 18 and Table 19 & Table 20 for intermediate risk and poor risk patients, respectively.

Table 17. Intermediate-risk patients – Progression free survival based on IRRC – Secondary Definition

	NIVO+IPI (n=334)	**Sunitinib (n=333)**
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	

Key: CI, confidence interval; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival.
Notes: [a], NIVO+IPI over Sunitinib

Table 18. Intermediate-risk patients – Progression free survival based on IRRC – Secondary Definition, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI, number at risk										
[redacted]										
Sunitinib, number at risk										
[redacted]										

Key: IRRC, independent radiology review committee; NIVO+IPI, nivolumab + ipilimumab.

Table 19. Poor-risk patients – Progression free survival based on IRRC – Secondary Definition

	NIVO+IPI (n=91)	Sunitinib (n=89)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	

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Key: CI, confidence interval; IRRC, independent radiology review committee; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival **Notes:** [a], NIVO+IPI over Sunitinib

Table 20. Poor-risk patients – Progression free survival based on IRRC – Secondary Definition, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI, number at risk										
[redacted]										
Sunitinib, number at risk										
[redacted]										
Key: IRRC, independent radiology review committee; NIVO+IPI, nivolumab + ipilimumab.										

A11. For the primary definition of investigator-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data requested in Table 21 & Table 22 and Table 23 & Table 24 for intermediate risk and poor risk patients, respectively.

Please be aware that for the hazard ratio reported in Table 21, the same logic would apply as explained in question A7. Hazard ratio is a better measure of the separation between the curves since the hazard ratio is an estimate of the totality of the time frame whereas the median is only a measure at one time point. The separation of the KM curves (explaining the HR) is shown in Figure 2.

Table 21. Intermediate-risk patients – Progression free survival based on Investigator assessment - Primary Definition

	NIVO+IPI (n=334)	**Sunitinib (n=333)**
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival **Notes:** [a], NIVO+IPI over Sunitinib		

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Figure 2. Kaplan-Meier plot of progression free survival based on investigator assessment - Primary definition

Table 22. Intermediate-risk patients – Progression free survival based on Investigator assessment – Primary Definition, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI, number at risk										
Sunitinib, number at risk										
Key: NIVO+IPI, nivolumab + ipilimumab.										

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Table 23. Poor-risk patients – Progression free survival based on Investigator assessment - Primary Definition

	NIVO+IPI (n=91)	Sunitinib (n=89)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival Notes: [a], NIVO+IPI over Sunitinib		

Table 24. Poor-risk patients – Progression free survival based on Investigator assessment – Primary Definition, number at risk

Months									
0	3	6	9	12	15	18	21	24	27
NIVO+IPI, number at risk									
[redacted]									
Sunitinib, number at risk									
[redacted]									
Key: NIVO+IPI, nivolumab + ipilimumab.									

A12. For the secondary definition of investigator-assessed PFS, please provide the number of events and median PFS in each arm of the trial, and hazard ratio (95% confidence intervals) for (i) intermediate-risk group patients and (ii) poor-risk group patients.

Please find the data requested in Table 25 & Table 26 and Table 27 & Table 28 for intermediate risk and poor risk patients, respectively.

Table 25. Intermediate-risk patients – Median progression free survival based on Investigator assessment – Secondary Definition

	NIVO+IPI (n=334)	Sunitinib (n=333)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival. **Notes:** [a], NIVO+IPI over Sunitinib		

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Table 26. Intermediate-risk patients – Progression free survival based on Investigator assessment – Secondary Definition, number at risk

Months										
0	3	6	9	12	15	18	21	24	27	30
NIVO+IPI, number at risk										
[redacted]										
Sunitinib, number at risk										
[redacted]										
Key: NIVO+IPI, nivolumab + ipilimumab.										

Table 27. Poor-risk patients – Median progression free survival based on Investigator assessment – Secondary Definition

	NIVO+IPI (n=91)	**Sunitinib (n=89)**
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard Ratio[a]	[redacted]	
Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival. **Notes:** [a], NIVO+IPI over Sunitinib		

Table 28. Poor-risk patients – Progression free survival based on Investigator assessment – Secondary Definition, number at risk

Months									
0	3	6	9	12	15	18	21	24	27
NIVO+IPI, number at risk									
[redacted]									
Sunitinib, number at risk									
[redacted]									
Key: NIVO+IPI, nivolumab + ipilimumab.									

A13. Table 9 of the company submission reports the IRCC-assessed ORR findings for intermediate-/poor-risk patients. Please provide the equivalent data for each arm of the trial for (i) intermediate-risk group patients and (ii) poor-risk group patients.

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Please find the data requested in Table 29 and Table 30 for intermediate risk and poor risk patients, respectively.

Table 29. Intermediate-risk population: Best overall response in CheckMate 214

	NIVO+IPI (n=334)	Sunitinib (n=333)
Best overall response (RECIST v1.1)		
Complete response		
Partial response		
Stable disease		
Progressive disease		
Unable to determine		
Not reported		
ORR, n (%)		
95% CI		
Difference of ORR, % (95% CI)		
p-value		

Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate.

Table 30. Poor-risk population: Best overall response in CheckMate 214

	NIVO+IPI (n=91)	Sunitinib (n=89)
Best overall response (RECIST v1.1)		
Complete response		
Partial response		
Stable disease		
Progressive disease		
Unable to determine		
Not reported		
ORR, n (%)		
95% CI		
Difference of ORR, % (95% CI)		
p-value		

Key: CI, confidence interval; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate.

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A14. A breakdown of subsequent treatment received on disease progression is presented for all patients in the CheckMate 214 trial in Table 13 of the company submission. Please provide a similar table for (i) intermediate-risk group patients and (ii) poor-risk group patients in each arm of the CheckMate 214 trial.

Table 31. Intermediate-risk population: Subsequent cancer therapy in CheckMate 214

	NIVO+IPI (n=334)	Sunitinib (n=333)
Any subsequent therapy, n (%)		
Subsequent radiotherapy, n (%)		
Subsequent surgery, n (%)		
Subsequent systemic therapy, n (%)		
ALK/EGFR tyrosine kinase inhibitors, n (%)		
Erlotinib		
Anti-CTLA-4, n (%)		
Ipilimumab		
Anti-PD-1, n (%)		
Nivolumab		
Pembrolizumab		
Anti-PD-L1, n (%)		
Atezolizumab		
Other immunotherapy, n (%)		
IFN		
IFN-α		
IL-2		
Investigational immunotherapy		
Other systemic cancer therapy – chemotherapy, n (%)		

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	NIVO+IPI (n=334)	Sunitinib (n=333)
Other systemic cancer therapy – experimental drugs, n (%)		

Key: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; NIVO+IPI, nivolumab + ipilimumab; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1.

Table 32. Poor-risk population: Subsequent cancer therapy in CheckMate 214

	NIVO+IPI (n=91)	Sunitinib (n=89)
Any subsequent therapy, n (%)		
Subsequent radiotherapy, n (%)		
Subsequent surgery, n (%)		
Subsequent systemic therapy, n (%)		
ALK/EGFR tyrosine kinase inhibitors, n (%)		
Erlotinib		
Anti-CTLA-4, n (%)		
Ipilimumab		
Anti-PD-1, n (%)		
Nivolumab		
Pembrolizumab		
Anti-PD-L1, n (%)		
Atezolizumab		
Other immunotherapy, n (%)		
IFN		
IFN-α		
IL-2		
Investigational immunotherapy		

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	NIVO+IPI (n=91)	Sunitinib (n=89)
Other systemic cancer therapy – chemotherapy, n (%)	[redacted]	[redacted]
Other systemic cancer therapy – experimental drugs, n (%)	[redacted]	[redacted]

Key: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; IFN, interferon; IL, interleukin; NIVO+IPI, nivolumab + ipilimumab; PD-1, programmed death receptor-1; PD-L1, programmed death receptor ligand-1.

A15. Please clarify why the incidence of some adverse events (AEs) in Table 16 of the company submission is different to the incidence of the same AEs in Table 15 of the company submission. Is this because not all immune-mediated AEs in Table 16 are necessarily considered to be treatment-related in Table 15?

Immune-mediated AEs (IMAEs) are defined as specific events, regardless of causality, occurring within 100 days of the last dose, and include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash and endocrine disorders; these are provided in Table 16 for the CheckMate 214 study. Table 15 presents drug-related AEs, defined as an AE with a reasonable causal relationship to study drug administration, as determined by a physician. Not all drug-related AEs will also be defined as IMAEs, hence the difference in incidence between the two tables.

Network meta-analysis

A16. **Clarification request sent to the company in advance of this letter (13 February 2018).**

The ERG makes the following observations:

- The NMA is constructed from a very large network of 37 trials, and includes a base-case analysis, 2 sensitivity analyses involving meta-regression and a secondary analysis for each outcome (overall survival [OS] and progression-free survival [PFS]) in order to obtain estimates of efficacy for NIVO+IPI versus pazopanib using various methods. For OS, none of these methods are able to derive a hazard ratio in the relevant patient population (patients with intermediate-/poor-risk advanced renal cell carcinoma [RCC]) for NIVO+IPI versus pazopanib.

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- Since the CheckMate 214 trial links NIVO+IPI to sunitinib, and the COMPARZ trial links sunitinib to pazopanib, the ERG considers that it would be possible to obtain estimates of efficacy (OS and PFS) for NIVO+IPI versus pazopanib in the relevant patient population from one network involving only the CheckMate 214 (NIVO+IPI versus sunitinib) and COMPARZ (pazopanib versus sunitinib) trials, assuming the necessary data were available.

- The ERG note that the company were able to extract a hazard ratio (with 95% confidence intervals [CI]) for PFS for patients with intermediate-/poor-risk advanced RCC in the COMPARZ trial but were unable to extract a hazard ratio for OS for the same population. The ERG has been unable to identify the source from where the hazard ratio for PFS is derived.

- In addition, the ERG notes that the company refers to report of the COMPARZ trial by Motzer et al 2014 (see Table 11, page 48 of the company's submission). The ERG notes that the OS data presented in the table are updated OS data (HR=0.92; 95% CI: 0.79 to 1.06) as opposed to the data reported by Motzer et al 2013 (hazard ratio=0.91; 95% CI, 0.76 to 1.08). The company have the earlier OS data (Motzer et al 2013) in their NMA.

As a result of the observations above, the ERG has the following queries:

Answers to the questions below are a copy of what have been submitted to the ERG and NICE on 16 February 2018.

1. For PFS, for patients with intermediate-/poor-risk advanced RCC, from which source was the hazard ratio for pazopanib versus sunitinib derived?

The HR for PFS for patients with intermediate risk advanced RCC was derived from Figure S3 (page 9) of the supplementary appendix of the COMPARZ trial (Motzer RJ et al., 2013)[2]. Figure S3 presents the forest plot of progression-free survival benefit across favourable and intermediate Memorial Sloan Kettering Cancer Centre (MSKCC) risk subgroups, the individual studies, and the per protocol analysis.

To obtain the HR and CI for pazopanib versus sunitinib using the intermediate MSKCC risk group only for pazopanib (n=650), Get Data Graph digitizer version 2.26 was used to extract the data. Please note that the forest plot in Figure S3 only presents data for the favourable and intermediate MSKCC risk subgroups since these were the only two MSKCC risk groups pre-specified in the PFS subgroup analyses (as noted by the authors in the supplementary methods section on page 5). MSKCC poor risk patients were excluded from the pre-specification analyses due to the expected small sample size and not available for analysis.

2. Did this source not include OS data for the same patient population?

The main publication of the COMPARZ trial[2] only reported the HR for the Intention-to-Treat population (n= 1,110, HR = 0.91; 95% CI, 0.76 to 1.08; P = 0.28) and did not report any subgroup analyses for OS.

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Similarly in the supplementary appendix only the Kaplan-Meier estimates for overall survival for the primary analysis population were presented. As such no data by risk prognosis subgroups was available for OS in the COMPARZ trial publication.

BMS acknowledges that updated OS results from the COMPARZ trial were published subsequently to the main publication as a letter to the editor[3]. Letters were however part of SLR exclusion criteria and as such the evidence from the letter was ultimately not included in the network meta-analysis (NMA).

BMS will re-run the full NMA incorporating the evidence contained within the letter to the editor and also provide a simpler Bucher indirect comparison as requested. These results will be provided by the specified date of 8th March.

3. If relevant data for OS were not presented in the source from which the HR for PFS was derived, did the company attempt to contact the authors of the COMPARZ trial for the relevant OS data?

BMS can confirm that the authors of the COMPARZ trial were not contacted to obtain OS data by risk prognosis subgroups.

Following on from its observations and queries, the ERG makes the following requests:

a. For PFS, please consider conducting a simpler indirect comparison for NIVO+IPI versus pazopanib and NIVO+IPI versus sunitinib using only the data from the CheckMate 214 and COMPARZ trials.
b. For OS, please consider conducting a simpler indirect comparison for NIVO+IPI versus pazopanib and NIVO+IPI versus sunitinib using only the data from the CheckMate 214 and COMPARZ trials if it is possible to obtain a HR for OS for the intermediate-/poor-risk patient population. Please use the most recent OS data where possible.

A17. **Priority question.** Following the company's response to question A16, the ERG requests that the company performs the following indirect comparisons using data from only the COMPARZ and CheckMate 214 trials.

a) For OS, the ERG requests that the company performs indirect comparisons using data from the letter by Motzer et al. (2014),[3] and the CheckMate 214 trial data in the following patient populations:

i. poor-risk patient population

An Indirect Treatment Comparison (ITC) was conducted using Bucher's method[4], as requested by the ERG. To summarise the approach, the log HR of two indirectly connected treatments A and C through treatment B can be obtained using the formula below:

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$$\ln\left(HR_{A,C}\right) = \ln\left(HR_{A,B}\right) - \ln\left(HR_{C,B}\right)$$

And its standard error is given by:

$$SE(ln\left(HR_{A,C}\right)) = \sqrt{SE(ln\left(HR_{A,B}\right))^2 + SE(ln(HR_{C,B}))^2}$$

In this scenario analysis, the inputs of the ITC were the OS HR for nivolumab with ipilimumab versus sunitinib [redacted][5] in the IMDC poor-risk RCC population from CheckMate 214 and the OS HR for pazopanib versus sunitinib (HR=0.85; 95% CI: [0.56, 1.28]) in the MSKCC poor-risk RCC population from the COMPARZ trial.[3]

The ITC HR for nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

The ITC results are however associated with significant limitations. The lack of patient characteristics reported by MSKCC subgroup in the COMPARZ publication prevents the comparison of patient demographics between the COMPARZ and CheckMate 214 poor-risk RCC patient populations. Therefore, potential bias due to unbalancing of treatment confounders between the two populations might exist which could bias the results of the ITC. Furthermore, neither trial was designed to obtain powered results on the poor-risk RCC population. The poor-risk population represented 16% (180 out of 1096) of the enrolled population in CheckMate 214, while representing 19% in the COMPARZ trial (119 out of 1110 patients).

ii. intermediate-risk patient population

An ITC was conducted using Bucher's method, as requested by the ERG. The method has been described in question A.2.a.i.

In this scenario analysis, the inputs for the ITC were the OS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate-risk RCC population from CheckMate 214 and the OS HR for pazopanib versus sunitinib (HR=0.90; 95% CI: [0.74, 1.09]) in the MSKCC intermediate-risk RCC population from the COMPARZ trial.[3]

The ITC HR for nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

As in the poor-risk population, the ITC results were associated with significant limitations. Patient characteristics were not available by MSKCC subgroup in the

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COMPARZ publication, therefore preventing the assessment of heterogeneity between the COMPARZ and CheckMate 214 intermediate-risk population and introducing potential bias in the analysis. Furthermore, neither of the trials was designed to obtain powered results in the intermediate-risk RCC population. The intermediate-risk population represented 61% (667 out of 1,096 patients) of the enrolled population in CheckMate 214, while representing 59% (650 out of 1,110) in the COMPARZ trial.[3]

iii. Intermediate-/poor-risk patient population (an estimate of HR for this patient population within the COMPARZ trial may be obtained by performing random-effects meta-analysis of the HRs reported for poor-risk and intermediate-risk patient groups separately).

As a first step, the OS HRs between pazopanib versus sunitinib were pooled together using the inverted variance weighting method[6] to obtain the HR between pazopanib versus sunitinib in the intermediate-and poor-risk patient population. The method can be summarised as following:

$$\ln(HR_{pooled}) = \frac{\sum wt_i \ln(HR_i)}{\sum wt_i}$$

with the weight of $\ln(HR_i)$ defined as $wt_i = 1/SE(\ln(HR_i))$.

And its standard error given by:

$$SE(\ln(HR_{pooled})) = \frac{1}{\sum wt_i}$$

The inputs for the pairwise meta-analysis were the OS HRs for pazopanib versus sunitinib in the MSKCC poor-risk [redacted] (HR=0.85; 95% CI: [0.56, 1.28]) and intermediate-risk (HR=0.90; 95% CI: [0.74, 1.09]) RCC populations from the COMPARZ trial.[3]

The pooled HR in the MSKCC intermediate/poor-risk patient population for pazopanib versus sunitinib was 0.89 (95% CI: [0.75 to 1.06]).

As a second step, an ITC was conducted using Bucher's method, which has been described in question A.2.a.i.

In this scenario analysis, the inputs for the ITC were the OS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate/poor-risk RCC population from CheckMate 214 and the OS HR for pazopanib versus sunitinib (pooled HR=0.89; 95% CI: [0.75, 1.06]) in the MSKCC intermediate-/poor-risk RCC population derived from the first step. The

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95% CI for the OS HR from CheckMate 214 were derived from the 99.8% CI, as shown in the formula below:

$$se(\ln(HR)) = (\ln(99.8\%\ upper\ CL) - \ln(99.8\%\ lower\ CL))/(2 * z_{0.01})$$

$$95\%\ Confident\ Limits = \exp(\ln(HR) \mp se(\ln(HR)) * z_{0.025})$$

The ITC HR for nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab. The HR was statistically significant with its [redacted] not including 1.

The result of the ITC was associated with three major limitations. The first one was the lack of an available published HR for the pooled intermediate/poor-risk population from the COMPARZ trial. An estimator was obtained by aggregating the HRs from the intermediate-risk and the poor-risk RCC populations. However, this method did not allow for adjustment of the different proportions of patients in the subgroups as the method only weighted by the variance of the estimate and not by any other factor/covariate. In addition, patient characteristics were not available by MSKCC subgroup in the COMPARZ publication, therefore not allowing for the assessment of heterogeneity between the COMPARZ and CheckMate 214 intermediate/poor-risk RCC populations and introducing potential bias in the analysis. Furthermore, the COMPARZ trial was not designed to obtain powered results on the intermediate/poor-risk RCC population. The intermediate- and poor-risk population represented 69% (769 out of 1,110 patients) of the patient population in the COMPARZ trial.[3]

b) For IRRC-assessed PFS, the ERG requests that the company performs 2 indirect comparisons using:

   i. the HR for the intermediate-risk patient population from the supplementary appendix of the COMPARZ trial,[2] and the CheckMate 214 trial data for the intermediate-risk patient population

   i.a Intermediate HR from CM 214 with IRRC assessed PFS using primary definition (censoring of subsequent treatment)

An ITC was conducted using Bucher's method. The method has been described in question A.2.a.i.

In this scenario analysis, the inputs for the ITC were the PFS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate-risk RCC population using the IRRC primary definition

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from CheckMate 214 and the PFS HR for pazopanib versus sunitinib '(HR=0.98; 95% CI: [0.80, 1.19]) in the MSKCC intermediate-risk RCC population from the COMPARZ trial.[3]

The ITC HR for nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

As for the previous ITCs, the ITC results were associated with significant limitations. Patient characteristics were not available by MSKCC subgroup in the COMPARZ publication, not allowing for the assessment of heterogeneity between the COMPARZ intermediate-risk population and the CheckMate 214 intermediate-risk population. Also, neither trial was designed to obtain powered results on the intermediate-risk RCC population. The intermediate-risk population represented 61% (667 out of 1,096 patients) of the enrolled population in CheckMate 214, while representing 59% (650 out of 1,110 patients) in the COMPARZ trial. Furthermore, the definition of PFS in the COMPARZ and CheckMate 214 trials might be different. Difference in outcome definition could cause bias in the ITC results due to transitivity hypothesis being violated.

i.b. Intermediate HR from CM 214 with IRRC assessed PFS using secondary definition (no censoring of subsequent treatment)

An ITC was conducted using Bucher's method. The method has been described in question A.2.a.i.

In this scenario analysis, the inputs for the ITC were the PFS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate-risk RCC population using the IRRC secondary definition from CheckMate 214 and the PFS HR for pazopanib versus sunitinib (HR=0.98; 95% CI: [0.80, 1.19]) in the MSKCC intermediate-risk RCC population from the COMPARZ trial.[3]

The ITC HR for nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

The same limitations as described in question i.a. apply to this analysis.

ii. the HR for the intermediate-risk patient population from the supplementary appendix of the COMPARZ trial,[2] and the CheckMate 214 trial data for the intermediate-/poor-risk patient population.

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ii.a Intermediate/Poor (combined) HR from CM 214 with IRRC assessed PFS using primary definition (censoring of subsequent treatment)

An ITC was conducted using Bucher's method. The method has been described in question i.a.

In this scenario analysis, the inputs for the ITC were the PFS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate-/poor-risk RCC population using the IRRC primary definition from CheckMate 214 and the PFS HR for pazopanib versus sunitinib (HR=0.98; 95% CI: [0.80, 1.19]) in the MSKCC intermediate-risk RCC population from the COMPARZ trial.[3] The 95% CI for the PFS HR from CheckMate 214 were derived from the 99.1% CI, as shown in the formula below:

$$se(\ln(HR)) = (\ln(99.1\%\ upper\ CL) - \ln(99.1\%\ lower\ CL))/(2 * z_{0.0045})$$

$$95\%\ Confident\ Limits = \exp(\ln(HR) \mp se(\ln(HR)) * z_{0.025})$$

The ITC HR between nivolumab with ipilimumab versus pazopanib was [redacted] in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

As for the previous ITCs, the ITC result was associated with significant limitations. The first major limitation was the inconsistent population definition as the ITC was performed using the PFS HR for nivolumab with ipilimumab versus sunitinib in the intermediate- and poor-risk patients while the PFS HR between pazopanib and sunitinib was evaluated only in the intermediate-risk population. In addition, the definition of PFS in the COMPARZ and CheckMate 214 trials might be different which could cause bias in the ITC results due to transitivity hypothesis being violated.

ii.b Intermediate/Poor (combined) HR from CM 214 with IRRC assessed PFS using secondary definition (no censoring of subsequent treatment)

An ITC was conducted using Bucher's method. The method has been described in question A.2.a.i.

In this scenario analysis, the inputs for the ITC were the PFS HR for nivolumab with ipilimumab versus sunitinib [redacted] in the IMDC intermediate-/poor-risk RCC population using the IRRC secondary definition from CheckMate 214 and the PFS HR between pazopanib versus sunitinib (HR=0.98; 95% CI: [0.80, 1.19]) in the MSKCC intermediate-risk RCC population from the COMPARZ trial[6].

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The ITC HR between nivolumab with ipilimumab versus pazopanib was [redacted], in favour of nivolumab with ipilimumab, despite not being statistically significant (95% CI including 1).

The same limitations as described in question II.a. apply to this analysis.

Please conduct each of the above indirect comparisons using both the primary and secondary definitions of PFS for the CheckMate 214 trial.

A18. **Priority question.** In the company's initial response to A16, the company states that the HR for pazopanib versus sunitinib for PFS for patients with intermediate risk advanced RCC was derived from Figure S3 of the supplementary appendix of the COMPARZ trial publication, using graph digitising software.

In Appendix D to the company submission (Table 5), the company presents data inputs for the NMA. Here, the HR for pazopanib versus sunitinib favours sunitinib in terms of PFS, whereas in Figure S3 of the supplementary appendix of the COMPARZ trial publication, the HR for pazopanib versus sunitinib clearly favours pazopanib. Please clarify, has the PFS HR for intermediate-risk patients been incorrectly extracted and incorporated in the conducted NMAs? If so, please ensure this error is addressed when performing the ERG requested indirect comparisons.

BMS acknowledges that the previous extraction was conducted erroneously due to the use of an incorrect log-scale. An updated extraction was performed using a different software to account for the log-scale used in the publication. The new HR (HR=0.98; 95%CI: [0.80, 1.19]) was furthermore validated using visual adequacy. All the ERG-requested analyses described above have been carried out with the updated PFS HR for pazopanib versus sunitinib.

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Section B: Clarification on cost-effectiveness data

B1. **Priority request.** Please provide in a separate document the Kaplan-Meier analyses listed in a) to h) and to the following specifications:

- Study data set: CheckMate 214 study, August 2017 data cut (or more recent if available).
- Format: please present analysis outputs using the format of the sample table provided at the end of section B (to include censoring times).
- Population: intermediate- and poor-risk population including all patients who were lost to follow-up or withdrawing from the trial.
- Stratification: all Kaplan-Meier analyses to be stratified by treatment and by risk group (intermediate and poor risk).

a) Time to death from any cause (OS) stratified by i) treatment and intermediate risk and ii) treatment and poor risk.

In the reference pack you will find two CSV documents with time to death from any cause in the format requested:

1. Intermediate risk population (stratified by treatment): *Question B.1.a_Intermediate_rg-ef-osb*
2. Poor risk population (stratified by treatment)*: Question B.1.a_Poor_rg-ef-osc*

b) Investigator-assessed PFS (primary definition). All patients who received subsequent systemic anti-cancer therapy prior to or without documented progression to be censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

In the reference pack you will find two CSV documents with investigator PFS (primary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.b_Intermediate_rg-ef-pfsinvpb*
b. Poor risk population (stratified by treatment)*: Question B.1.b_Poor_rg-ef-pfsinvpc*

c) Investigator-assessed PFS (secondary definition). All patients who did not progress or die to be censored on the date of the last evaluable tumour assessment, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

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In the reference pack you will find two CSV documents with investigator PFS (secondary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.c_Intermediate_rg-ef-pfsinvsb*

b. Poor risk population (stratified by treatment)*: Question B.1.c_Poor_rg-ef-pfsinvsc*

d) IRRC-assessed PFS (primary definition). All patients who received subsequent systemic anti-cancer therapy prior to or without documented progression to be censored at the date of the last tumour assessment conducted on or prior to the initiation of the new therapy, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

In the reference pack you will find two CSV documents with IRRC-assessed PFS (primary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.d_Intermediate_rg-ef-pfsirrcpb*

b. Poor risk population (stratified by treatment)*: Question B.1.d_Poor_rg-ef-pfsirrcpc*

e) IRRC-assessed PFS (secondary definition). All patients who did not progress or die to be censored on the date of the last evaluable tumour assessment, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

In the reference pack you will find two CSV documents with IRRC-assessed PFS (secondary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.e_Intermediate_rg-ef-pfsirrcsb*

b. Poor risk population (stratified by treatment)*: Question B.1.e_Poor_rg-ef-pfsirrcsc*

f) Post-progression survival (PPS) based on investigator-assessed PFS, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

The number of events and the number of patients for post-progression survival (based on investigator assessed PFS) can be obtained from the PFS and OS data, as requested in question B.1.b and B.1.a. To find the relevant data: In the reference pack you will find two CSV documents with investigator PFS (primary definition) in the format requested:

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a. Intermediate risk population (stratified by treatment): *Question B.1.b_Intermediate_rg-ef-pfsinvpb*

b. Poor risk population (stratified by treatment)*: Question B.1.b_Poor_rg-ef-pfsinvpc*

c. Intermediate risk population (stratified by treatment): *Question B.1.a_Intermediate_rg-ef-osb*

d. Poor risk population (stratified by treatment)*: Question B.1.a_Poor_rg-ef-osc*

For investigator PFS, secondary definition, the PPS can be obtained from the PFS and OS data requested in question B.1.c and B.1.a. In the reference pack you will find two CSV documents with investigator PFS (secondary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.c_Intermediate_rg-ef-pfsinvsb*

b. Poor risk population (stratified by treatment)*: Question B.1.c_Poor_rg-ef-pfsinvsc*

c. Intermediate risk population (stratified by treatment): *Question B.1.a_Intermediate_rg-ef-osb*

d. Poor risk population (stratified by treatment)*: Question B.1.a_Poor_rg-ef-osc*

g) PPS based on IRRC-assessed PFS, stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

The number of events and the number of patients for post-progression survival (based on IRRC- assessed PFS, primary definition) can be obtained from the PFS and OS data, as requested in question B.1.d and B.1.a. To find the relevant data: In the reference pack you will find two CSV documents with IRRC-assessed PFS (primary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.d_Intermediate_rg-ef-pfsirrcpb*

b. Poor risk population (stratified by treatment)*: Question B.1.d_Poor_rg-ef-pfsirrcpc*

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c. Intermediate risk population (stratified by treatment): *Question B.1.a_Intermediate_rg-ef-osb*

d. Poor risk population (stratified by treatment)*: Question B.1.a_Poor_rg-ef-osc*

For IRRC investigated PFS, secondary definition, the PPS can be obtained from the PFS data requested in question B.1.e and B.1.a. In the reference pack you will find two CSV documents with investigator PFS (secondary definition) in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.e_Intermediate_rg-ef-pfsirrcsb*

b. Poor risk population (stratified by treatment)*: Question B.1.e_Poor_rg-ef-pfsirrcsc*

c. Intermediate risk population (stratified by treatment): *Question B.1.a_Intermediate_rg-ef-osb*

d. Poor risk population (stratified by treatment)*: Question B.1.a_Poor_rg-ef-osc*

h) Time to study treatment discontinuation (TTD), stratified by stratified by (i) treatment and intermediate risk and (ii) treatment and poor risk.

In the reference pack you will find two CSV documents with TTD in the format requested:

a. Intermediate risk population (stratified by treatment): *Question B.1.h_Intermediate_rg-ef-durtrtb*

b. Poor risk population (stratified by treatment)*: Question B.1.h_Poor_rg-ef-durtrtc*

B2. On page 79 of the company submission it states that: "…the log-normal model provided the best statistical fit to each stratified dataset. However, given the immaturity of the OS data and different extrapolation projections of each parametric model, parametric model selection was based primarily on the clinical plausibility of projected OS over the lifetime horizon."

The log-normal model was rejected and the log-logistic model was chosen for OS in the base case based on clinical opinion that 5-year survival would be:

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- around 15%-20% for treatment with sunitinib, based on the results of the global expanded-access study reported by Gore et al 2015.[7]

- around 35%-45% for treatment with NIVO+IPI.

Please justify why the log-logistic model for treatment with NIVO+IPI was chosen when each of the 7 independently-fitted models produced 5-year estimates of OS between 33%-44%, and all but the gamma and Weibull models produced estimates of between 35%-44%.

Please also provide further justification as to why the log-logistic model for treatment with sunitinib was chosen when 4 of the 7 independently-fitted models (gamma, exponential, Weibull and Gompertz) produced 5-year estimates of OS between 15%-20%, but the log-logistic model produced a 5-year OS estimate of 24%.

These requests are perhaps most easily addressed with reference to CheckMate 214 sunitinib arm OS extrapolations first.

To clarify, Dr Larkin's advice was to use the data reported by Gore et al.[7] to justify sunitinib OS curve selection, while his instinct in absence of careful consideration of these data was a 5-year survival probability of 15-20%.

As such, after meeting with Dr Larkin, we considered the Gore et al. data carefully in order to help inform curve selection, as opposed to solely using Dr Larkin's instinctive estimate. Through digitisation of the KM data reported in Figure 2 of Gore et al.[7] (using the GetData digitizer software[8]), we estimated 5-year survival for intermediate-risk patients to be 25.6% and for poor-risk patients to be 5.5%. These data are provided in Column CJ to CW of the OS sheet in the submitted cost-effectiveness (CE) model. In the CheckMate 214 primary endpoint sample, 58% of patients were baseline intermediate-risk and 18% were baseline poor-risk (page 11 of Document B from the company submission). Assuming the intermediate-/poor-risk patient split in CheckMate 214 is representative of the NHS England RCC patient group who stand to benefit from NIVO/IPI, and the Gore et al. data to be representative of NHS England sunitinib patient survival, the best 5-year survival estimate for sunitinib intermediate-/poor-risk patients can be calculated as 20.8%:

18%/(18%+58%) * 5.5% + 58%/(18%+58%) * 25.6%

The 5-year survival predictions for the 7 parametric models fitted to CheckMate 214 sunitinib OS data are shown in Table 33.

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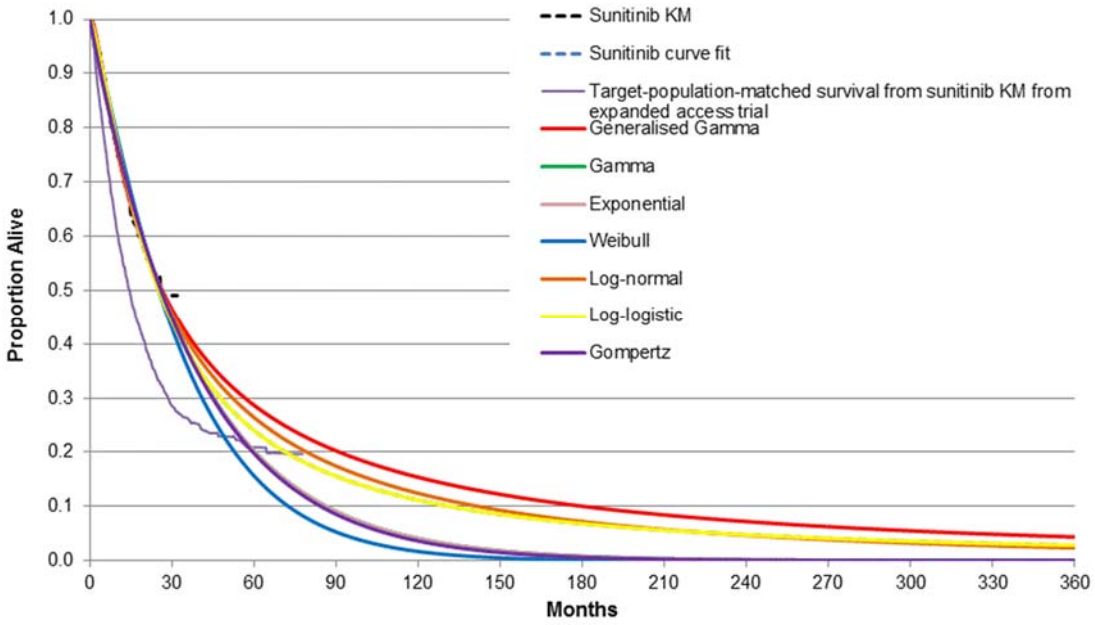
Table 33: Independent curve fit overall survival estimates for the sunitinib arm

Parametric curve	5-year overall survival estimate
Exponential	20.4%
Gamma	16.1%
Generalised gamma	28.8%
Gompertz	19.9%
Log-logistic	24.1%
Log-normal	26.5%
Weibull	15.8%

Exponential and Gompertz models provide the closest approximation to the target Gore et al. 5-year survival estimate, while the log-logistic model estimate is higher. At this point, consider the longer-term extrapolations of the different models, in relation to the longer-term data from Gore et al. (CS, Figure 19) and the nature of RCC. The slope of the exponential and Gompertz model fits tend towards zero in line with the shape properties of these models, while the log-logistic model projection has a far shallower gradient, that reflects both the Gore et al. data up to its ~78-month end, and biological rationale for long-term RCC survival, even in the absence of immune-checkpoint-inhibitor (ICI) treatment.

Figure 3: Sunitinib independent OS curve fits and Gore et al. data (adapted from Figure 19 of Document B in the CS)



Key: CS, company submission; KM, Kaplan–Meier; OS, overall survival.

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An abbreviated description of this decision is given in Cell K71 of the Controls sheet of the submitted CE model, but should be corrected to read:

Based on survival estimates from Gore et al., 2015 (5-year OS of 25.6% and 5.5% for intermediate- and poor-risk patients, respectively), and CheckMate 214 intermediate-/poor-risk patient characteristics (76.3% intermediate- and 23.7% poor-risk, respectively), long-term real-world data would suggest 20.8% of sunitinib patients should be alive at 5 years. Log-logistic provides one of the closest extrapolations to this, with a good statistical fit.

Here, we feel the use of the log-logistic model fit to CheckMate 214 OS data to capture sunitinib OS could be considered sufficiently justified for an academic exercise, but for the purposes of this appraisal, consider also the Decision Support Unit Technical Support Document (DSU TSD) (14) guidance on parametric modelling of RCT KM data when a proportional hazards assumption is problematic:

"Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two-dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis." (page 39-40)[9]

Now, let us turn to the most appropriate model for CheckMate 214 NIVO+IPI OS extrapolation. For clarity, the 7 parametric fits to CheckMate 214 NIVO+IPI OS data and their respective 5-, 10- and 15-year survival estimates are shown in Figure 2 and Table 34.

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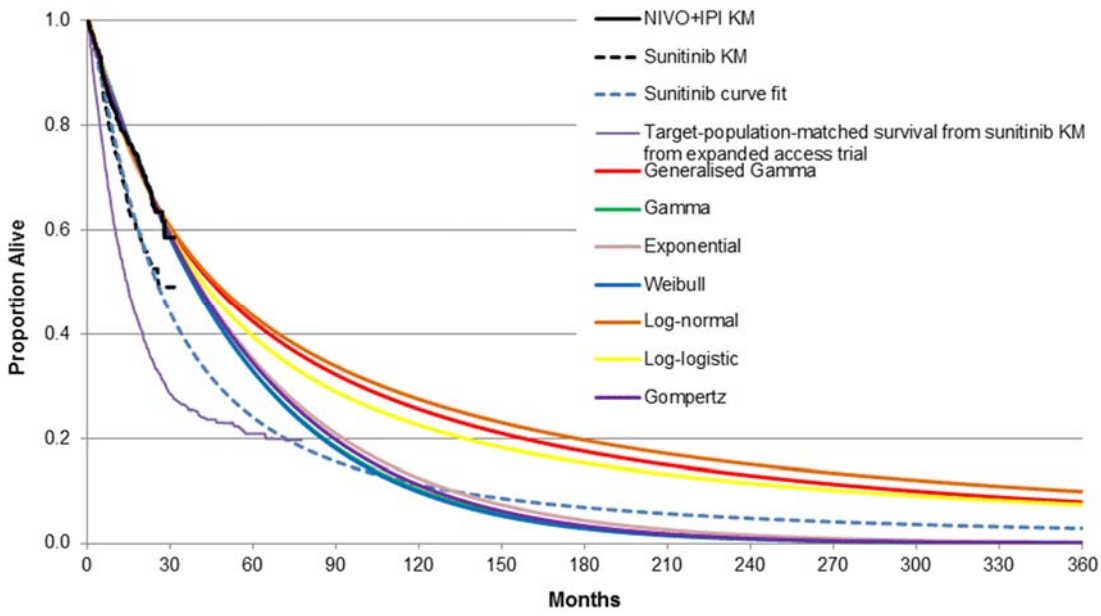
Figure 4: NIVO+IPI independent OS curve fits and Gore et al. data (adapted from Figure 19 of Document B in the CS)



Key: CS, company submission; KM, Kaplan–Meier; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival.
Notes: Log-logistic fit used for the sunitinib arm.

Table 34: Independent curve fit overall survival estimates for the NIVO+IPI arm

Parametric curve	5-year OS estimate	10-year OS estimate	15-year OS estimate
Exponential	35.3%	12.4%	4.4%
Gamma	33.1%	10.2%	3.1%
Generalised gamma	42.5%	25.6%	17.6%
Gompertz	34.6%	11.2%	3.3%
Log-logistic	39.6%	22.5%	15.3%
Log-normal	43.6%	27.5%	19.7%
Weibull	33.0%	9.8%	2.8%
Key: NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival.			

From Table 34 (data also shown graphically in Figure 17 of Document B from the Company Submission (CS)), and in line with the different properties of the 7

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statistical models, the exponential, Weibull, Gompertz and gamma models tend towards zero with a gradient that is at odds with the biological rationale and evidence for ICI treatment in RCC patients, and RCC patients generally, as evidenced in Section B.3.3.2 of the CS. Of the remaining models (log-logistic, generalised gamma and log-normal), the log-logistic provided the most plausible fit to the sunitinib OS data, as discussed above. Given the quoted DSU TSD 14 guidance, in the absence of "substantial justification", it seems reasonable to use the log-logistic model across treatment arms. Of the log-logistic, log-normal and generalised gamma models, the log-logistic is also the most conservative, predicting the smallest lifetime area under the NIVO+IPI OS curve.

All this said, it could be argued that there is "substantial justification" to consider a less optimistic survival extrapolation for sunitinib patients versus NIVO+IPI patients, particularly when the cost-utility analysis controls separately for expected immunotherapeutic survival benefit for patients who go on to receive nivolumab monotherapy after sunitinib. In this case, the CS base case approach can surely be considered conservative. Ceteris paribus, amending the CS base case by selecting an exponential model fit to comparator OS data reduces the deterministic ICER estimate (versus sunitinib) from XXXXX per QALY gained to xxxxx per QALY gained.

In summary, we hope that The Review Group can be reassured that curve selection was carefully considered, with reference to wider evidence and rationale and not solely the helpful advice of Dr Larkin, and that the choices arrived at were logical, in line with the conservative approach of the submission, and consideration of advice in NICE DSU TSD 14.

B3. Table 18 in the company submission summarises OS in CheckMate 003, CheckMate 010 and CheckMate 025. Please clarify whether the values reported in Table 18 refer to the ITT population in the 3 studies mentioned or whether they refer to the intermediate-/poor-risk subgroup.

If the values in Table 18 refer to the ITT population, please produce a similar table for the intermediate-/poor-risk subgroup using the most up-to-date data cuts for each trial.

To answer this question, a full analysis of the datasets is needed. As we did focus on the analysis done in Checkmate 214, time did not allow us to do these analysis or look if the analysis were possible. Therefore, this question will be answered at a later time.

B4. The company models an immunotherapeutic effect on the basis of durable response. On page 32 of the company submission, the company estimates that of 30.1% of patients treated with NIVO+IPI were durable responders in CheckMate 214, based

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on the proportion of patients who had responded to treatment with NIVO+IPI and were still responding by the time of the August 2017 data cut.

The ERG understands from this that the company links the notion of durable response to ORR and PFS, as ongoing response indicates that no progression event has occurred (except potentially immunotherapy–induced "pseudo progression"). However, the company appears to model a long-term survival effect for treatment with NIVO+IPI for OS alone. Please clarify how the notion of durable response and long-term survival are linked.

We acknowledge that should an immunotherapeutic effect exist, and be predicted by durable response, it is likely to impact both PFS and OS. However, conservatively, only an effect on overall survival was included in the cost-effectiveness model, considering both clinical opinion and how this long-term survival mechanism was implemented in the nivolumab second-line NICE submission (TA417).[10]

Should there be an immunotherapeutic effect on both PFS and OS, we are uncertain as to what the extent of the PFS effect would be relative to OS, but as PFS is not a big driver of results in this case, we would not expect this to significantly change the model outcome. This is because utility and treatment costs are dependent on the modelled patient's time on treatment, rather than progression-free survival.

B5. On page 124 of the company submission, it states that "[redacted]

In Table 43, assumption 13 it states that" Those patients who have a durable response to NIVO+IPI have the potential for an immune checkpoint inhibitor quality of life and survival benefit without the need for further toxic systemic treatment".

Given that the company models 30% of patients treated with NIVO+IPI to be durable responders who will not require further therapy, please explain why a further [redacted] of patients who are not durable responders are also assumed not to receive further therapy following discontinuation of treatment.

We assumed that [redacted] of patients who discontinue NIVO+IPI are too ill to receive any further treatment. The effect of varying the assumed proportion of patients receiving subsequent treatment upon cost-effectiveness results was tested in both one-way sensitivity analysis (Figure 36 on page 154 of Document B from the CS) and scenario analysis (Table 48 on page 158 of Document B from the CS).

B6. On page 124 of the company submission, it states that "[redacted], by which the ERG infers that it is

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assumed that [redacted] of patients treated with sunitinb do not receive subsequent therapy.

In Table 43, assumption 13, it states that “all patients who withdraw from sunitinib treatment who are fit enough for subsequent active treatment are expected to receive further treatment”.

Please confirm whether or not this means that all patients who do not receive subsequent therapy after discontinuing treatment with sunitinib, do not receive it because they are too ill to do so.

We can confirm that the model assumes that [redacted] of patients who do not receive subsequent therapy after discontinuing treatment with sunitinib are too ill to receive any further treatment. The effect of varying the assumed proportion of patients receiving subsequent treatment upon cost-effectiveness results was tested in both one-way sensitivity analysis (Figure 36 on page 154 of Document B from the CS) and scenario analysis (Table 48 on page 158 of Document B from the CS).

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Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0`.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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Section C: Textual clarifications and additional points

C1. Please provide the statistical analysis plan (SAP) for CheckMate 214.

The statistical plan can be found in the reference pack, uploaded to the NICE documents page

C2. In Table 7 of the company submission (page 26), it is stated that "At the time of database lock, the number of deaths was half of the total OS events, so an adjusted alpha of 0.002 was applied (to provide 98% CI)." Should the statement instead be "to provide 99.8% CI"?

Yes, the CI was incorrectly written in the company submission. The statement should instead read "to provide 99.8% CI".

C3. In the legend for Table 7 of the company submission, IRRC is defined as "Immune Related Response Criteria". Elsewhere in the submission, IRRC is defined as "independent radiology review committee". Please clarify whether the definition in Table 7 of the company submission is correct.

The definition in Table 7 of the company submission is incorrect. This should in fact read "Independent radiology review committee".

C4. **Priority question.** We request that you reconsider the information labelled as confidential in your submission and economic model. To ensure that the appraisal process is as transparent as possible, NICE considers it essential that evidence on which the Appraisal Committee's decisions are based is publicly available. With this in mind please could you reconsider the following specific sections:

Data marked 'Academic in Confidence' due to EMA regulatory timelines

NICE does not publish documents prior to positive Committee for Medicinal Products for Human Use (CHMP) approval. Therefore, please consider removing the confidentiality of 'academic in confidence' data which would be lifted at the point of positive EMA regulatory approval.

Cost-effectiveness results marked 'commercial in confidence'

Throughout the submission all components of the cost-effectiveness results are redacted. Please consider reporting transparently the incremental cost-effectiveness ratios (ICERs), as this is key to showing the evidential basis of the committee decision.

Subsequent treatment use assumptions marked 'commercial in confidence'

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Throughout the submission you have marked assumptions about the subsequent treatment use, which are informed by clinical opinion, as 'commercial in confidence'. Please consider lifting the confidentiality of these assumptions, as we do not believe that they can be used to back-calculate the confidential discount for nivolumab if the total costs and QALYs are confidential.

Please resubmit your submission by 5pm Thursday the 8th March and include a revised and fully completed Checklist of Confidential Information stating, for each piece of information, the rationale for treating it as confidential and the expiry date of that confidentiality.

Thank you for raising this issue, and the spirit in which your request is intended. Please appreciate that with you, we appreciate the merits of the Institute's decision-making process and its emphasis on public transparency. We aim to support this, but at the same time have to be mindful to maintaining the level of confidentiality pivotal to price discount agreements that allow us to offer our most innovative technologies to as many NHS England patients as possible. The academic-in-confidence markings in our submission were similarly made only to allow us to disseminate our findings through other avenues. Due to time restrictions, we weren't able to unmark any data that will be published in the EPAR. We will come back to this request at a later stage.

Regarding commercial-in-confidence markings in Section B.3, reference was made in the 26 February 2018 clarification tele-conference to the confidentiality labelling in TA490, and how a similar approach might be used for the materials in this appraisal. The approach to confidentiality marking in TA490 was broadly to redact cost and utility parameter values, total intervention costs and QALY estimates, and incremental cost and QALY estimates (intervention versus each comparator). This allowed ICER estimates to be publicly visible, and can be seen as roughly the inverse of the approach to confidentiality we have taken in this submission, with similar levels of confidentiality marking, just in different areas. Deciding which is the more transparent approach involves value judgements, yet we understand if the ERG have a preference for the ICER-visible approach in TA490. Nevertheless, we are concerned that we cannot take this approach in this appraisal while maintaining the confidentiality of our PAS agreement for nivolumab, due to the publicly available information in TA417, and the consistency of our approach in this appraisal with that in TA417. We would understand if the ERG had not considered this when making this request.

We would like to stress that had less burden been placed upon us at this stage, we would have liked to have devoted more time and resource to exploring this issue, which we do recognise as important.

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C5. Please can you clarify in Table 15 (page 55) of the appendices to the company submission whether the first mentioned Motzer 2013 study refers to the COMPARZ trial (sunitinib versus pazopanib) and the second mentioned Motzer 2013 study refers to the TIVO-1 trial (tivozanib versus sorafenib)?"

This should be the other way around, the first mentioned Motzer 2013 study refers to the TIVO-1 trial (tivozanib vs sorafenib) and the second mentioned Motzer 2013 study refers to the COMPARZ trial.

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References

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID1182]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Cancer Support Network
3. Job title or position	Head of Medical Relations
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors Rose Woodward and Julia Black, who started by providing practical and bespoke support to individual patients for access to life-extending cancer drugs to treat metastatic kidney cancer. Empowering patients to take an active role in their own health care, and, more generally, in decisions affecting the choice, provision and quality of cancer services throughout the UK, remains the top priority for KCSN. Over the years, KCSN has grown considerably, with a membership of over 1000 kidney cancer patients and carers, and a further 800+ active and committed patients and carers on its confidential social networking sites. KCSN is unique; until recently it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it raise the funds to better meet the growing needs of the kidney cancer community. KCSN is funded by grants from trusts/foundations/grant-making organisations and the pharmaceutical industry, in addition to donation from patients and fundraising events/activities carried out by the kidney cancer community in the UK.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	When gathering the information for this submission, we specifically asked for patient and carer experience of using the nivolumab pus ipilimumab combination through our closed social media channels. We have a dedicated immunotherapy Facebook group specifically set-up to help us collate experiences from patients using these types of medication. Over 800 patients and carers use these channels to communicate on a

carers to include in your submission?	regular basis, and we receive in the order of 500 posts a day on our closed Facebook group.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Kidney Cancer Support Network (KCSN) is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in the strongest position to feedback how metastatic renal cell carcinoma (mRCC) affects the day-to-day lives of people living with this disease. In 2014, there were more than 12,500 new cases of kidney cancer diagnosed in the UK (34 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people (2014). Kidney cancer accounts for 3% of all new UK cancer cases (2014). In 2014, nearly 4,500 people died from the disease and about 40% of kidney cancer patients will be diagnosed with late stage disease. In these cases, it is estimated that around only 10% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this. Metastatic RCC is a devastating disease and is currently incurable. The majority of mRCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings with it enormous financial pressures for the patient and their family (and additional costs to the state) and can precipitate psychological problems; depression, loss of confidence and self-worth. Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other more rare sites. Patients with bone metastases are at risk of bone breaks and spinal cord compression. Metastases in the lungs can lead to breathlessness, and persistent coughing, while spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised and patients find daily living difficult, often needing periods of rest during the day. Patients diagnosed with hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options. Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time.

	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, a process of elimination is used to select the most effective treatment for individual patients. Clinicians in the UK should have the ability to choose the optimal treatments for individual patients from those available. Without a choice of treatment alternatives, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in therapy to continue managing their disease, and to maintain quality of life. Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental as well as physical clinical situation. Sexual function is affected for both male and female patients, and family life suffers as a result. Kidney cancer cases are rising year-on-year and there is a need for first-line treatment with better overall survival rates than currently exist, especially for difficult-to-treat rare subtypes of RCC. The impact of a terminal diagnosis on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a terminal disease.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The current treatment pathway for mRCC is surgery (either radical or partial nephrectomy), followed by either sunitinib or pazopanib in the first-line setting, and axitinib, everolimus, cabozantinib or lenvatinib plus everolimus in the second-line setting, all of which are oral medicines and have similar modes of action (tyrosine kinase inhibitors (TKIs) or mTOR inhibitors that block angiogenesis). Nivolumab is also recommended for use within NHS England for second- or third-line treatment of mRCC, and is the first third-line treatment in use by the NHS. Nivolumab is an immunotherapy (anti-PD-1), which is administered as a biweekly intravenous infusion, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer. We have extracted the following details from statements submitted to the KCSN by patients living with mRCC. Using currently available drugs, many patients suffer with the following side effects, all of which severely affect quality of life:

	• Extreme fatigue • Severe hand and foot syndrome which can leave patients unable to walk • Intestinal problems (chronic diarrhoea) • Pneumonitis requiring hospital treatment and cessation of treatment • Severe mouth ulcers causing problems eating and drinking • Nausea and vomiting, which can also cause problems taking the medication • High blood pressure (hypertension) • Hyperthyroidism All the above side effects require additional medicines to help patients manage the drugs and/or tumour pain, which require opioid prescriptions. Costs for additional medicines to mitigate the side effects of these targeted therapies should be taken into account. Other less serious side effects, which still affect the patient's quality of life, are loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment as a result of severe side effects. Patients are aware that these treatments are life-extending drugs, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life. For patients that have been on standard first-line treatment with TKIs and experienced severe side effects, combination immunotherapy could see a dramatic change in quality of life: *"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."* *"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." *"When I began treatment I was in a state of helplessness. The abdominal tumour was located in such a position that it was growing so fast and 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 confined to a wheelchair. I was unable to carry out even basic tasks and from being a very physically strong man who was very active and worked on my small ranch, I could do nothing for myself. I was very ill; I was told I had about 12 months to live. Tumours were growing aggressively."* For most patients, the most important treatment outcome would be no evidence of disease, i.e., a potential cure for their kidney cancer. The hope of achieving this outcome spurs patients on to continue to take current medication, despite significant toxicity, and to search for alternative, more effective treatments that can extend overall survival. Failing to achieve no evidence of disease, tumour shrinkage or disease stability would be the next best outcome for patients. In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities: *"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 ……. 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".* *"…….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……".*

	Although less serious than some of the side effects to current first-line treatments, some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and also singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels. From a psychological point of view, knowing that you have stage 4 cancer and knowing that there are possibly more effective treatments that you are not able to access is very difficult for patients. Carers seem to find this even harder, as they live with a guilt of not being able to do everything they can for their loved one. Access to a choice of treatments in the first-line would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient. Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities; international discussion forums exist where patients talk to one another daily, and patients are more aware of the experiences of others, including their access to innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity. Information about immunotherapies is readily available to patients around the world on websites, such as www.10forio.info. Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England to improve outcomes, so that patients in England have the same choices as patients in other countries.
8. Is there an unmet need for patients with this condition?	There is an unmet need for a first-line treatment that improves overall survival and allows patients to live a good quality of life without the incumbent debilitating side effects of current first-line treatments. There is also a significant unmet need for effective and safe treatments for people with hereditary kidney cancer or rare RCC subtypes, who currently have very limited treatment options.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nivolumab has been proven to be a clinically effective and well-tolerated drug, and designated a breakthrough therapy by the FDA for the treatment of advanced or metastatic RCC. 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. The nivolumab plus ipilimumab combination is the first immunotherapy combination to show efficacy in metastatic RCC, and has been granted priority review status by the FDA. Patients and carers opinions of the nivolumab plus ipilimumab combination are based on their experience of nivolumab monotherapy in the second-line setting, and immune checkpoint inhibitors in general. They are hopeful that the combined immunotherapy with nivolumab plus ipilimumab will improve survival compared to current first-line treatments. This is borne out by the results from the CheckMate-214 study of nivolumab plus ipilimumab, which showed a greater objective response rate (41.6% versus 26.5%) and prolonged progression-free survival (11.6 months versus 8.4 months) compared to sunitinib in intermediate- and poor-risk patients with previously untreated advanced or metastatic RCC. In addition, they also see the combined immunotherapy as being better tolerated than standard first-line treatments, resulting in improved quality of life and the promise of living a normal life and contributing both socially and economically to society. The following quotes are taken from RCC patients on nivolumab monotherapy, but give good examples of how this particular drug has dramatically changed the lives of these patients: *"In about two months of commencing treatment, the pain began to subside and very shortly ceased completely. This was the first indication Nivolumab was working. The improvement in my quality of life was 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 are minimal on my quality and enjoyment of life. Obviously the change in my health has impacted the life of my wife. I can now care for myself in every way and be a help to her. I am*

	no longer dependent on any one. I can put in a full day of hard physical work on the ranch on all but the day following treatment." *"Whereas the side effects from sunitinib were bearable I found that for axitinib these were definitely not. Although I was on a minimum dosage over a 12-month period from April 15 I lost 25 kg as I couldn't eat or drink. I also suffered from severe tiredness and upset stomach ....basically the drug was much too toxic and was killing me. Within 2 weeks of stopping axitinib I was back to normal with eating and drinking and living a more normal life style. I have yet to show any side effects from Nivolump [sic] although I still need to go to bed earlier than I used to do! I have only had 8 iva sessions so side effects maybe lurking around the corner! Long may they lurk!"* *"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."* *"….. my husband started on Axitinib. We had hoped this drug would work well but the treatment was stopped …. when my husband developed severe sepsis. We were extremely fortunate that this happened when Nivolumab became available under EAMS. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk. Axitinib caused diarrohea, severe blistering to feet and mouth and we had to seek help from a chiropodist to try and enable him to walk but even she couldn't help him. In all my husband lost 5 stone in weight during his time on TKIs. Since his starting on Nivolumab, my husband's health has improved dramatically, he eats well and has started to put on weight again. Even though he is 66 years of age he works 5 days a week and now can enjoy his pastime of fishing on Saturday and Sunday. My husband has a very strong character but even he struggled with the side effects of Axitinib."* *"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." *"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 …… 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."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We understand that nivolumab and ipilimumab are both expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug combination available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding mechanism, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug combination. The combination immunotherapy is given intravenously every 3 weeks for 4 doses (12 weeks) followed by nivolumab monotherapy until disease progression or drug intolerance. This requires hospital visits every 3 weeks during the first 3 months, followed by every 2 weeks thereafter, and the provision of chemotherapy chairs for the infusion, which can last up to 2.5 hours for the combination immunotherapy. Standard first-line treatment with oral TKIs only require a monthly hospital visit to replenish supplies of medication, and

	can be taken at home. Patients will typically be travelling some distance to a regional cancer centre for the immunotherapy infusions. Some patients may need to take time off work, or have a partner travel with them to treatments, the practical aspects of which can impact the quality of life of both patient and carer. However, balanced against the extra travel and time is the improved 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 debilitating side effects of TKIs.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues	
13. Are there any other issues that you would like the committee to consider?	Nivolumab and ipilimumab are the first in a new class of immunotherapy drugs. 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 the 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 possible care. 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 other kidney cancer patients in the rest of Europe and North America. A contributory factor to poor survival rates in the UK is possibly due to the restrictions in clinical choice brought about by UK regulatory authorities. In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and without this immunotherapy combination, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the first-line, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life. Current first-line treatment options are not effective for everyone. Undue restrictions in accessing immunotherapy would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The nivolumab plus ipilimumab combination is the first immunotherapy combination to show efficacy in metastatic RCC, and has been granted priority review status by the FDA
- The nivolumab plus ipilimumab combination is well tolerated, as well as proven to be more effective at extending progression-free survival and improving overall response rates compared to standard first-line treatment with sunitinib
- Adding the nivolumab plus ipilimumab combination as a choice in the first-line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life
- The improved tolerability of the nivolumab plus ipilimumab combination enhances quality of life and enables patients to contribute socially and economically to society
- The nivolumab plus ipilimumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

Patient organisation submission

Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID1182]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	Communications Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading charity dedicated to research into kidney disease in the UK. We rely almost wholly on the generous donations of the UK public and we believe that everybody deserves a life free of kidney disease.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	We have gathered patient experiences and information from our lay patient advisers and other clinical advisers via phone and email communication. In addition, we have reviewed other patient forums on the topic.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Symptoms can include extreme tiredness, weight loss, significant back pain, high temperatures, night sweats, anaemia and high blood pressure which makes daily living difficult Diagnosis can be delayed or missed because some symptoms can be similar to the symptoms of other conditions, which means patients are often confused, angry and frustrated as a result. Patients are understandably frightened and fearful about the future for themselves and their family. Patients can feel like they are a burden on their families. Family members wish they could help but are fearful for a future without their loved one. For patients, hope is vitally important. (www.kidneycancersupportnetwork.co.uk)
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel there aren't enough options regarding treatments, or flexibility in treatments.

8. Is there an unmet need for patients with this condition?	Kidney cancer is a silent condition in which the symptoms appear at a later stage. Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence occurring in Western countries. There has been an annual increase of about 2% in incidence both worldwide and in Europe with overall mortality rates increasing. Kidney cancer is the eighth most common cancer in adults in the UK, with 9,286 new cases diagnosed in 2009 and 3,848 deaths from kidney cancer in 2008. This accounts for over 2% of all cancer deaths in the UK. In UK men, it is the sixth most common cancer, with 5,706 new cases diagnosed in 2009, and in UK women it ranks ninth with 3,580 new cases diagnosed in 2009. This is a male to female ratio of approximately 3:2 for incidence in the UK. It has been estimated that the lifetime risk of developing kidney cancer is 1 in 56 for men and 1 in 90 for women (Cancer Research UK last accessed 4/1/18). http://webarchive.nationalarchives.gov.uk/20160105160709 Special consideration needs to be given to patients with an uncommon cancer, as in kidney cancer, who are disadvantaged from diagnosis. Patients and clinicians would like access to a drug that slows down, halts or reverses tumour growth; which offers people hope, more time with their families and time to make provisions for their loved ones. There remains a significant unmet need for treatment options that offer ongoing responses and increase survival for patients with renal cell carcinoma, the most common type of kidney cancer.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Any drugs (single or in combination) that can extend the patient's life will have a positive impact on family relations and dynamics and their ability to live independently and enjoy life at home and with their family. This is an important aspect, as constant reliance on other people tends to make patients feel helpless and affects their confidence, whilst long stays in a hospital setting can make them feel isolated and institutionalised. Nivolumab + ipilimumab (CTLA-4 antibody) combination therapy (NIVO + IPI) has shown manageable safety and high anti-tumour activity and at nearly two years follow up 40% of patients had an ongoing response rate.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients (and their carers) with this uncommon cancer are generally more willing to accept more adverse events for a greater survival benefit and an overall improvement in Quality of Life (QOL) The safety profile is manageable and is comparative to other therapies for RCC. This combination is administered IV and may not suit all patients In studies 22% of patients discontinued the treatment due to adverse events, however 80% of patients received the four courses without serious adverse events The most common side effects were; fatigue (33%), nausea (14%) and severe itching (14%) for nivolumab, and fatigue (34%), inflammation of the mucous membrane of the mouth (30%) and anaemia (24%) for everolimus.

	http://www.esmo.org/Conferences/Past-Conferences/European-Cancer-Congress-2015/News/Nivolumab-Improves-Overall-Survival-in-Patients-with-Advanced-Kidney-Cancer-results-from-the-CheckMate-025-trial
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	In the key phase III trial (CheckMate-025) which evaluated nivolumab and ipilimumab, demonstrated that in **intermediate and poor-risk patients** with previously untreated advanced or metastatic renal cell carcinoma found an overall survival benefit. The results of CheckMate-025 show for the **first time** an immuno-oncology agent in combination has demonstrated an overall survival advantage in renal cell carcinoma, in a patient group that currently has limited treatment options, versus sunitinib which is the current standard of care,) in RCC patients. This combination is administered IV and may not suit all patients.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	There are few effective treatment options for this rare cancer and any new treatment combination or single therapy that offers an improved response rate over current standard of care offers patients with RCC hope for the future.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Diagnosis can be delayed or missed because some symptoms can be similar to the symptoms of other conditions, which means patients are often confused, angry and frustrated as a result.
- Patients are understandably frightened and fearful about the future for themselves and their family.
- Nivolumab + ipilimumab (CTLA-4 antibody) combination therapy (NIVO + IPI) has shown manageable safety and high anti-tumour activity and at nearly two years follow up 40% of patients had an ongoing response rate.
- The safety profile is manageable and is comparative to other therapies for RCC.
- There are few effective treatment options for this rare cancer and any new treatment combination or single therapy that offers an improved response rate over current standard of care offers patients with RCC hope for the future.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission on the NICE appraisal of the combination of nivolumab and ipilimumab in the treatment of metastatic renal cell adenocarcinoma

1. If NICE recommends the combination of nivolumab and ipilimumab in the treatment of metastatic renal cell adenocarcinoma, NHS England will commission this solely as 1st line treatment as the key phase III evidence comes from the comparison of this combination with one of the options of standard 1st line chemotherapy.
2. If NICE recommends the combination of nivolumab and ipilimumab in the treatment of intermediate and poor risk metastatic renal cell adenocarcinoma, this will have an effect on the treatment pathway so as to displace current 1st line options to 2nd line and current 2nd line options to 3rd line options. Thus 2nd line treatment options would become one choice of 3 TKIs ie of pazopanib or sunitinib or tivozanib and third line treatment options become one choice of cabozantinib or axitinib or the combination of lenvatinib plus everolimus or everolimus monotherapy. BMS and the ERG are therefore incorrect in their assumptions as to what patients would be treated with on failure of the 1st line combination of nivolumab and ipilimumab. NICE and the EMA may have previously issued recommendations and licenses respectively based on the use of words such as 'first line' or 'second line'. Such statements are victims of time in terms of the then treatment pathway. What are more important considerations for the present are evaluation of modes of action of treatments and any previous statement by NICE/EMA as to the need for previous TKI therapy: these govern NHS England's commissioning intentions.
3. BMS assumes a 2nd line treatment rate of 60% in the nivolumab/ipilimumab treatment pathway and 80% in the current treatment pathway after pazopanib/sunitinib/tivozanib. These numbers are wrong. The two published studies of 2nd line treatment rates after treatment with a 1st line TKI demonstrated figures of 42% and 57% in 2014 and 2015, respectively. NHS practice remains conservative as compared with Europe and the USA and hence a 2nd line treatment rate of 50% is appropriate in 2018.
4. NHS England sees no convincing rationale for why BMS assumes a much higher 2nd line treatment rate for patients treated with 1st line TKI especially when this rate (80%) is so much greater than 50%. This erroneous assumption of 80% does of course have a significant impact on the health economics as BMS assumes that an absolute 60% of 1st line starters with a TKI go on to receive (costly) nivolumab.
5. NHS England expects therefore that on the present evidence post 1st line treatment with nivolumab/ipilimumab, 50% of patients will receive 2nd line treatment and most patients will receive pazopanib (60% and rising) rather than sunitinib (40% and falling). Tivozanib would also be an option as it has recently been recommended by NICE but there appear to be drug supply problems.
6. NHS England expects in the current treatment pathway post 1st line TKI therapy, 50% of patients go on to receive 2nd line therapy. Of these, 60% receive nivolumab, 20-

25% receive cabozantinib, 10-15% axitinib and a few are treated with lenvatinib plus everolimus.

7. NHS England considers that the overall survival data in the nivolumab/ipilimumab RCT are immature, particularly for consideration of the longer term outcome for when it is hoped the combination of nivolumab and ipilimumab will be producing a tail on the survival curve. The median duration of follow up is 25 months and there are few patients at risk beyond 27 months: the data are immature as to observe what the long term tail is on the survival duration plot.
8. Sunitinib has significant side effects although most of these are short term as they can be ameliorated by dose delays and dose adjustments. The side-effect profile of sunitinib is worse than that of pazopanib, hence the steadily rising use of pazopanib rather than sunitnib 1st line. The side-effect profile of the nivolumab/ipilimumab combination appears attractive but there are uncommon yet important and serious toxicities with this combination with longer term use (pneumonitis, colitis, nephritis, hepatitis and endocrinopathies). Whilst the lower dose of ipilimumab in this combination versus the higher dose in melanoma will offset some of these toxicities, NHS England is aware of the significant current impact of the nivolumab/ipilimumab combination in melanoma on non-oncology medical specialties and on acute admissions. NHS England notes that treatment discontinuation rates on account of drug toxicity was twice as high in the nivolumab/ipilimumab arm than in the sunitinib arm in a trial in which 70% of patients had a very high Karnofsky performance status (90-100%). The toxicity of this combination cannot therefore be lightly dismissed.
9. NHS England notes that the median survival duration for patients with intermediate risk metastatic disease is rising. In the International Metastatic Renal Carcinoma Database Consortium 2011 publication of patients in the intermediate risk group who were not treated with TKIs (1975-2002), the median survival was 11.5 months. When the IMRCDC model was tested in a population-based study of patients treated with TKIs in the period 2004-2010, the median survival duration of intermediate risk patients was 22.5 months (Lancet Oncol 2013; 14: 141-8). There are several new NICE-approved treatment options which have been brought into clinical practice since 2010. Hence NHS England considers that the median survival duration of the intermediate risk metastatic group will be at least 2 years and the mean survival duration substantially more than 2 years in this group. NHS England also notes that BMS modelled the mean survival of the intermediate and poor risk groups in the sunitinib control arm of Checkmate 214 study to be 4.5 years.
10. As NICE is aware, the majority of recent NICE recommendations have included 2 year stopping rules for anti-PD-1 and anti-PD-L1 drugs in lung cancer, urothelial cancer and head and neck cancer. This is therefore a clear trend in terms of NICE decision making but its acceptance by clinicians also reflects increasing clinical concern as to the longer term toxicities of such immunotherapy.

11. NHS England would urge NICE, when assessing whether the End of Life criteria apply to consideration of clinical and cost effectiveness, should use the same population of patients on which to base its conclusions as to the degree of benefit of treatment as well as survival duration. If lower life expectancies are used for NHS patients in assessing whether a higher cost effectiveness threshold applies or not, then it is only logical to assume lower degrees of benefit for NHS patients as well - but such evidence does not exist.
12. The ratio of intermediate to poor risk metastatic patients entered in clinical trials varies. The ratio in the nivolumab/ipilimumab RCT is 3.7. In the original 2011 publication of the International Metastatic Renal Carcinoma Database Consortium (2811 patients), the ratio was 2.0. In the latest 2013 validation of the IMRCDC stratification (692 patients), the ratio was 1.7. In the 2015 publication of the sunitinib global expanded patient access programme, the ratio was 2.5. The ratio in the COMPARZ sunitnib vs pazopanib trial was 4.8. It is thus difficult to know what the mix of intermediate to poor risk patients would be in NHS England. However, poor prognosis patients do much worse than intermediate risk patients and as 70% of patients in Checkmate 214 were of a very high performance status (KPS 90-100%), NHS England considers that it is likely that NHS clinicians will also select good performance status patients for treatment with nivolumab/ipilimumab and thus intermediate risk patients will also be preferentially treated on account of better performance status. NHS England therefore does not see a rationale for assuming that the mix of intermediate to poor patients in NHS practice will be very different from that observed in Checkmate 214.

Prof Peter Clark
NHS England Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund
May 2018

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma [ID1182]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Cancer UK
3. Job title or position	Patient Lead
4a. Brief description of the organisation (including who funds it). How many members does it have?	We provide support to patients and families of people with kidney cancer, raise awareness, run campaigns, provide information and fund research into kidney cancer. The organisation is funded by donations and each year we communicate with 3640 new patients.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We have no links with the tobacco industry
5. How did you gather information about the experiences of patients and carers to include in your submission?	I used our patient survey and listen to the views of patients and spoke to patients at our living with kidney cancer days and at our support groups. We also listened to patients on our closed facebook group.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Different people will react to living with kidney cancer differently and the challenges they face greatly depend on the stage of their disease. Most people with kidney cancer will receive surgery at some point, which will require a period of recovery. There will be times when the patient and family/carers will be worried about the future and require information and guidance. Waiting for news, scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort. Dealing with side effects of drugs can be equally exhausting as the symptoms of the cancer, so finding the balance of treatment and quality of life that is right for each patient is important.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatment and outcome are very much dependant on how early the kidney cancer has been caught. Ideally the tumour is of an early stage and is removed by surgery or cryotherapy and the patient enjoys a life after cancer. This would always be the preferred treatment. However, if the tumour has spread patients will rely on targeted therapies and immotherapy treatments. Current drug treatments for kidney cancer are very limited in number and have plenty of side effects. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects. The most commonly used Tyrosine kinase inhibitors (sunitinib and pazopanib) act to extend life and in some cases they work very well and extend life for many years. For others, the

	extension of life is a matter of months. However, those months can be invaluable for individuals and their families. The recent introduction of nivolumab (immunotherapy) as a NICE recommended 2nd line drug is very good news. Patients have reported back on how effective this drug has been for them especially their quality of life. I think that having combinations of treatments may give alternate options and even better results as a first line treatment. Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that Nivolumab in combination with ipilimumab works for a set of patients where other 1st line treatments may fail. A multitude of treatment options is always desirable.
8. Is there an unmet need for patients with this condition?	Yes there is an unmet need for treatment of advanced RCC it would most certainly improve some outcomes in patients surviving kidney cancer and to be free of cancer for the foreseeable future. We understand that most drug treatments aim to extend the lives of people with kidney cancer and viewing kidney cancer as a chronic disease that can be lived with would be a desirable outcome. Tolerable side effects of a treatment are important if kidney cancer is to be viewed as a chronic disease and patients are to have a good quality of life.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	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
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	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
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with advanced (stage 3 or 4) disease are likely to require TKI's to extend their life. People who have failed prior systemic treatment are likely to need another treatment option, which introducing Nivolumab in combination with ipilimumab will provide.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• None known

Other issues	
13. Are there any other issues that you would like the committee to consider?	What about patients that have another type other advanced renal cancer?

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- People with advanced kidney cancer have very few treatment options and require a variety of drug choices.
- Nivolumab in combination with ipilimumab has an acceptable and improved side effect profile compared to other first line drugs, which will improve people's quality of life and hopefully extend a patient's life.
- The future will hopefully be more development in immunotherapy and hopefully there will be better outcomes in survival rates and a better quality of life for patients living with advanced kidney cancer.
- Different drugs work for different people. A particular group of people may respond really well to Nivolumab in combination with ipilimumab where other TKI's and targeted therapies may not work for them as a first line treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal Marsden NHS Foundation Trust**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Control/potentially cure metastatic kidney cancer
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Dependent on clinical context
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Relevant NICE and other guidance
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Generally well defined
• What impact would the technology have on the current pathway of care?	Potentially significant impact on drug therapy for metastatic kidney cancer
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Broadly

• How does healthcare resource use differ between the technology and current care?	Currently nivolumab monotherapy is given 2nd line to patients that have failed 1st line VEGFR TKI therapy i.e. sunitinib/pazopanib. The combination of nivolumab and ipilimumab 1st line would stop the use of 2nd line nivolumab monotherapy and may mean that responding patients are never treated with VEGFR TKI therapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No further investment although there would likely be a greater demand on existing infrastructure e.g. day unit, admissions for side effects.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective for intermediate and poor risk advanced clear cell kidney cancer
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Similar

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Distinguishing good from intermediate/poor risk which is straightforward clinically
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Don't know
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes as above; improved overall survival in intermediate/poor risk disease
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are manageable and less severe than with the same combination in melanoma because of different ipilimumab dosing
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	Unknown at present
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Significant overall survival benefit in 1st line for the first time in the modern era of RCC management • Greatest benefit in intermediate and poor risk disease • Manageable side effects (and rate less than nivo + ipi in melanoma) • Possibility of long term disease control/cure including in patients, that have stopped the treatment •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Brighton and Sussex University Hospitals**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ a specialist in the treatment of people with this condition? ✓ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve the outcomes, in terms of response rates, length of response and overall survival, for patients receiving first line treatment for intermediate and poor risk advanced renal cancer.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The beneficial responses to this treatment would usually be measured by the impact on progression free survival and overall survival.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Sunitinib has been the standard of care for patients with this diagnosis for the past decade. Whilst the advances brought by this drug were very valuable, the overall outcome for patients remains poor. New therapies that bring significant improvement in response and survival would be welcomed by patients and clinicians.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The standard first line treatment for intermediate and poor risk advanced renal cancer currently a choice of the two TKI agents, Sunitinib and Pazopanib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are local Guidelines in addition to ESMO, EAU and NCCN guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The management of renal cancer in the UK follows a relatively standardised pathway across the NHS. Whilst there is a choice of 1st line TKI drug there is little evidence to suggest that these drugs differ in their efficacy.
• What impact would the technology have on the current pathway of care?	The new technology would fit within the current pathway of care. The only difference would be the administration of the new technology is more complex than the current standard.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The new technology is already in routine use in the NHS in the treatment of patients with advanced melanoma. Of the two component drugs of the new technology, Nivolumab used as a single agent is widely used in the treatment of other malignancies.

• How does healthcare resource use differ between the technology and current care?	The new technology is administered intravenously whilst the current care is an oral therapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This therapy would be prescribed and delivered in specialist oncology units.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The NHS is already routinely familiar with the use of this combination therapy and its component parts. The new technology would need an increase in nursing
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The published clinical trial data indicates an important improvements in response rates, progression free survival and overall survival.
• Do you expect the technology to increase length of life more than current care?	The published data indicates that patients treated with the new technology are likely to live longer

• Do you expect the technology to increase health-related quality of life more than current care?	Overall the toxicity impact of the new technology and Sunitinib are similar in terms of the likelihood of significant grade 3 or grade 4 technology. The licencing trial indicates that more patients discontinued the new technology rather than Sunitinib for adverse events (22% vs 12%)
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is not suitable for patients with good prognosis advanced renal cancer.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The new technology is given intra venously, whilst the current care is a tablet therapy. A change to the new technology will result in an increase in the work of the chemotherapy day unit team. However immunotherapy with treatments similar to this new technology are well established in the NHS and already form an important and growing part of treatment activity.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules for staring and stopping therapy will be very similar to those already in routine use.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	The published data indicates that the new technology produces higher response rates, improved progression free survival and enhanced overall survival than the current therapy for this patient group. Overall these components would make a substantial impact on health benefits.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The new technology is a significant change in treatment. It uses a new treatment modality for the first line therapy of renal cancer and the results show important benefits.
• Does the use of the technology address any particular unmet need of the patient population?	The benefits from treatment appear similar across the population of patients with intermediate and poor risk advanced renal cancer.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immunotherapy with immune check point inhibitors produces a different pattern of side effects from the current treatment. The identification and management of these problems is now becoming engrained in NHS oncology care. With early recognition and expert management the risks to determent to the patients quality of life are being reduced.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	The licencing trial used Sunitinib as the control arm. In the UK the first line therapy for renal cancer is currently shared relatively equally between Sunitinib and Pazopanib. These two drugs are regarded as interchangeable in their efficacy and the trial could fairly be judged as a comparison against either first line TKI.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trial data measures response rate, progression free survival, overall survival and toxicity.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	There have been a number of studies that give further evidence on the efficacy and tolerability of Sunitinib. These would include the COMPARZ and PISCES trials and real-world database studies such as published by Ruiz-Morales et al.
22. How do data on real-world experience compare with the trial data?	The real world and trial data are similar but the real world has more unwell, poor performance and elderly patients and slightly less impressive data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None apparent

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • First line immunotherapy in intermediate and poor risk renal cancer • Enhanced response rates, progression free survival and overall survival • Manageable side effects • Established therapy in other malignancies •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

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

Completed 10th April 2018

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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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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Tosin Lambe	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Rui Duarte	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the adverse event data
Eleanor Kotas	Cross checking of the submission search strategies
Joanne McEntee	Critical appraisal of the company submission
Richard Griffiths	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of this ERG report.

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LIST OF ABBREVIATIONS

1L	First-line
2L	Second-line
AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicine Strategy Group
BIC	Bayesian information criterion
CI	Confidence interval
CS	Company submission
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DoR	Duration of response
EMA	European Medicines Agency
EQ-5D	EuroQol Group 5-Dimensions questionnaire
EQ-5D-3L	EuroQol Group 5-Dimensions 3-levels questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IMAE	Immune-mediate adverse event
IMDC	The International Metastatic Renal Cell Carcinoma Database Consortium
IRRC	Independent radiology review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
K-M	Kaplan-Meier
KPS	Karnofsky performance status
LYG	Life year(s) gained
MSKCC	Memorial Sloan Kettering Cancer Center
NICE	National Institute for Health and Care Excellence
NIVO+IPI	Nivolumab in combination with ipilimumab
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein
PD-L1	Programmed death receptor ligand-1
PFS	Progression-free survival
PH	Proportional hazard
PPS	Post-progression survival
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life years
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SMC	Scottish Medicines Consortium
TA	Technology appraisal
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TTD	Time to treatment discontinuation, time to discontinuation
TTR	Time to response
Tx	Treatment
VEGFR-TKI	Vascular endothelial growth factor receptor-tyrosine kinase inhibitor
WTP	Willingness-to-pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Bristol-Myers Squibb in support of the use of nivolumab (Opdivo®) in combination with ipilimumab (Yervoy™), hereafter referred to as NIVO+IPI, for untreated advanced or metastatic renal cell carcinoma (RCC). NIVO+IPI has not yet received a marketing indication for the treatment of advanced RCC. The Committee for Medicinal Products for Human Use (CHMP) opinion, marketing authorisation and the European Public Assessment Report (EPAR) are all expected to be available in the second and third quarters of 2018.

1.2 Critique of the decision problem in the company submission

The anticipated indication for NIVO+IPI in relation to the current appraisal is: “for the treatment of adult patients with intermediate/poor risk advanced renal cell carcinoma”. It is specified in the NICE scope that risk should be defined using the International Metastatic RCC Database Consortium (IMDC) criteria. This is the model used to determine risk in the CheckMate 214 trial from which the majority of evidence for NIVO+IPI is derived. The ERG notes that many previously published trials have used the Memorial Sloan Kettering Cancer Center (MSKCC) model, including the previous CheckMate 016 trial of NIVO+IPI and a previous non-inferiority trial of pazopanib versus sunitinib (the COMPARZ trial). Of note, while the evidence for NIVO+IPI is derived entirely from previously untreated patients, as noted by the company, the anticipated licence may not specify that patients must be untreated (unlike the NICE scope). Based on current NHS clinical practice, the ERG considers sunitinib and pazopanib are the most appropriate comparators in the current appraisal. Clinical evidence is reported in the company submission (CS) for all five outcomes specified in the final scope: overall survival (OS), progression-free survival (PFS), response rates (including overall response rate [ORR]), adverse events (AEs) and health-related quality of life (HRQoL). As specified in the final scope issued by NICE, the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective. No subgroups were specified in the final scope issued by NICE.

1.3 Summary of the clinical evidence submitted by the company

The company carried out a systematic search of the literature in May 2017 to identify randomised controlled trials (RCTs) investigating the efficacy and safety of NIVO+IPI and comparator studies for the treatment of people with previously untreated metastatic RCC. RCTs that investigated the clinical efficacy and/or safety of a broader range of potential interventions than are available within NHS clinical practice were eligible for inclusion in the systematic review. The CheckMate 214 trial was the only trial that compared NIVO+IPI with one of the relevant comparators (sunitinib).

The CheckMate 214 trial is an ongoing phase III, randomised, open-label study of NIVO+IPI versus sunitinib in patients with previously untreated, advanced RCC with a clear-cell component. Patients were randomised in a 1:1 ratio to receive treatment with NIVO+IPI or sunitinib. From October 2014 through February 2016, 1096 patients were randomly assigned to treatment. Baseline characteristics of patients were well balanced between arms.

Although the trial included patients with favourable risk disease, the co-primary endpoints (OS, PFS and ORR) were analysed only in the combined intermediate/poor risk population (n=839), the population of relevance to the current appraisal. PFS and ORR were assessed in a blinded manner by the Independent Radiology Review Committee (IRRC). Investigator-assessed PFS and investigator-assessed ORR were also analysed as secondary outcomes. Of note, although the trial is ongoing, the data monitoring committee (DMC) recommended early termination of the trial for benefit when the planned first-interim analysis for OS was conducted. Results from the CheckMate 214 trial are presented in the CS from this first interim analysis (7 August 2017) for all outcomes.

Median patient follow-up was 25.2 months. Median OS was not reached in the NIVO+IPI arm (95% confidence interval [CI]: 28.2 to not evaluable [NE]) and was 26.0 months (95% CI: 22.1 to NE) in the sunitinib arm. The hazard ratio (HR) for OS demonstrated a statistically significant treatment effect for NIVO+IPI in comparison to sunitinib (HR=0.63, 99.8% CI: 0.44 to 0.89; p<0.001).

The company used two definitions of PFS: the primary definition, which included censoring for subsequent therapy, and the secondary definition, which did not include censoring for subsequent therapy. Median PFS (primary definition) in the CheckMate 214 trial was 11.6 months (95% CI: 8.8 to 15.5) in the NIVO+IPI arm and 8.4 months (95% CI: 7.0 to 10.8) in the sunitinib arm. The corresponding HR was not statistically significant (HR=0.82, 99.1% CI: 0.64 to 1.05), but was described by the company as being clinically meaningful. Results for IRRC-assessed PFS with and without censoring for subsequent therapy (i.e. primary and secondary

definitions) were similar. Investigator-assessed results for PFS showed similar HRs to the IRRC-assessed results (primary and secondary definitions).

The IRRC-assessed ORR was 41.6% (95% CI: 36.9 to 46.5) in the NIVO+IPI arm and 26.5% (95% CI: 22.4 to 31.0) in the sunitinib arm (p<0.0001). A complete response was seen in 40 (9.4%) NIVO+IPI patients and 5 (1.2%) sunitinib patients. At the time of analysis, 72% of responding patients in the NIVO+IPI arm had an ongoing response, in comparison to 63% of responding patients in the sunitinib arm. These patients were classified as "durable responders". Investigator-assessed ORR was consistent with ORR as assessed by IRRC.

As part of the clarification process, the ERG requested that the company provide efficacy data (OS, PFS and ORR) from the CheckMate 214 trial for intermediate and poor risk groups separately. The company states that the data presented for the OS HRs for both intermediate and poor risk groups indicate no evidence of a difference between the groups and there is a clear statistically and clinically meaningful OS benefit in both groups, individually and combined. They also highlight that there is a small difference in the PFS HR for the intermediate and poor risk subgroup; in this disease setting, PFS does not provide a great indicator of clinical benefit. However, the company considers that the results should be interpreted with caution, as the analyses were post-hoc analyses.

Pre-specified subgroup analyses by programmed death receptor ligand-1 (PD-L1) status show that patients in the intermediate/poor risk group with PD-L1 tumour expression ≥1% and those with PD-L1 tumour expression <1% have greater benefit (OS, PFS and ORR) with NIVO+IPI than with sunitinib. The company states that the findings support previous observations that PD-L1 is not a predictive biomarker for nivolumab effect in advanced RCC.

Compared to the sunitinib arm, in the NIVO+IPI arm, [redacted] patients experienced treatment-related AEs (TRAEs) ([redacted]) or Grade 3 to 4 TRAEs ([redacted]). [redacted] patients experienced treatment-related serious AEs (TRSAEs) ([redacted]) or Grade 3 to 4 TRSAEs ([redacted]). Discontinuations from TRAEs, reported only for the all risk population, were [redacted] in the NIVO+IPI ([redacted]) arm than in the sunitinib arm ([redacted]).

HRQoL was assessed by the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) for patients with intermediate/poor risk disease and the EuroQol 5-Dimension (EQ-5D) and Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires for all risk patients. Results show that HRQoL was [redacted] over time for patients treated with NIVO+IPI compared with patients treated with sunitinib based on all three instruments.

To enable a comparison of NIVO+IPI with pazopanib, the company conducted complex network meta-analyses (NMAs) including a large number of trials. At the ERG's request the company also performed indirect comparisons utilising data only from the CheckMate 214 trial and the COMPARZ trial. The results of the indirect comparisons suggest that NIVO+IPI improves OS (but not PFS) in comparison to pazopanib in the intermediate/poor risk patient population.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Overall, the ERG considers the methods used to conduct the clinical effectiveness systematic review to be satisfactory.

The ERG considers the population in the CheckMate 214 trial to be broadly similar to the population likely to be treated in NHS clinical practice. It is, however, noted that the patients are younger than would be seen in clinical practice and there were slightly more intermediate risk patients and slightly fewer poor risk patents than would likely be seen in clinical practice. The proportions in the trial were 61% with intermediate risk disease and 17% with poor risk disease. Clinical advice received by the ERG is that in clinical practice, proportions would be approximately 50% and 30%, respectively. In addition, clinical advice to the ERG is that the proportion of patients with prior nephrectomy in the CheckMate 214 trial (90%) may be slightly higher than the proportion expected to be seen in clinical practice (approximately 70%). Older patients, patients with clear cell disease, patients with poor risk disease and patients without nephrectomy are expected to have a worse prognosis than younger patients, patients with non-clear cell disease, intermediate risk disease and prior nephrectomy.

The ERG notes that the efficacy results presented for intermediate and poor risk groups separately appear to be broadly consistent with those reported for patients in the intermediate/poor risk group combined. The ERG agrees with the company that these results should be interpreted with caution, as the analyses were post-hoc analyses. Therefore, the results from the intermediate/poor risk group combined are considered to be the most appropriate results to consider for decision making, particularly given NIVO+IPI is anticipated to be licensed for this population as a whole. The ERG therefore considers results from the intermediate/poor risk group are the most appropriate results for cost effectiveness analysis, particularly considering the immaturity of the OS data.

The ERG notes that the CheckMate 214 trial was stopped early and OS data are immature: in the immediate/poor risk population, deaths had occurred in [redacted]% of patients in the NIVO+IPI arm and [redacted]% of patients in the sunitinib arm. There is evidence across various disease areas

that some trials (of various different treatments) that have been stopped early for benefit have not delivered the anticipated OS gain estimated at the time of stopping. The ERG notes that in a previous appraisal of nivolumab (for previously treated locally advanced or metastatic squamous non-small cell lung cancer, TA483), the CheckMate 017 trial was also stopped early for benefit on the recommendation of the DMC. In the CheckMate 017 trial, the 18-month (almost fully mature) efficacy data that subsequently became available appeared to support the DMC's decision to stop the trial early. Nonetheless, relative survival between the trial arms in the CheckMate 214 trial is based on immature data, and so the ERG considers that it is unknown whether the OS benefit observed at the first-interim analysis of OS will be observed in the longer-term.

Based on clinical advice to the company and ERG, it is expected that nearly all patients treated with NIVO+IPI would receive carbozantinib or axitinib on disease progression. The company (and ERG) also considers that patients treated with first-line sunitinib would mostly receive nivolumab on disease progression. However, in the CheckMate 214 trial, only [redacted] of patients in the NIVO+IPI arm received subsequent carbozantinib/axitinib and [redacted] in the sunitinib arm received subsequent nivolumab.

The ERG considers that censoring for the initiation of an effective anticancer treatment before progression occurs may be an example of informative censoring. Thus, an analysis of PFS without censoring is likely to be less prone to bias. Nonetheless, in the CheckMate 214 trial, the ERG notes that results reported for PFS with and without censoring for subsequent therapy (primary and secondary definitions, respectively) were similar.

The ERG notes that the Cox proportional hazards (PH) method was used to estimate the OS and PFS HRs for the CheckMate 214 trial. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time. From examining the Kaplan Meier (K-M) data, the ERG considers that the PH assumption may be violated for OS and PFS (primary and secondary definitions) in the intermediate/poor risk population. Consequently, the ERG considers that the reported HRs for OS and PFS data from the CheckMate 214 trial should be interpreted with caution.

While investigator-assessed results for PFS showed similar HRs to the IRRC-assessed results (primary and secondary definitions), median PFS was reported to be [redacted] in the NIVO+IPI arm using the primary definition ([redacted]) than the IRRC-assessed PFS (11.6 months). The ERG notes that the median investigator-assessed PFS using the secondary definition is not reported in the CS. The difference in median IRRC- and investigator assed PFS provides further evidence that the assumption of PH is violated.

Investigator assessed PFS using the secondary definition (without censoring for subsequent therapy) is preferred by the ERG for modelling cost effectiveness. The rationale for this is summarised in Section 1.6.

Clinical advice to the ERG is that the toxicity profiles of NIVO+IPI and sunitinib are very different and therefore make direct comparisons challenging. However, overall, NIVO+IPI appears to be less toxic than sunitinib. This is because many AEs associated with sunitinib tend to be chronic, whereas AEs with immune checkpoint inhibitors (such as NIVO+IPI) tend to occur sporadically and unexpectedly and are characteristically transient.

Results show that HRQoL was [redacted] over time for patients treated with NIVO+IPI compared to patients treated with sunitinib. However, as only patients who remained on treatment were asked to complete the questionnaires, the numbers of patients eligible to complete the questionnaires over time reduce markedly. Therefore, the results must be treated with a degree of caution, particularly results from 24 weeks and beyond.

For the ERG's requested indirect comparison of NIVO+IPI versus pazopanib using only two trials, the ERG is aware that risk status was assigned using the IMDC model in the CheckMate 214 trial and using the MSKCC model in the COMPARZ trial. The IMDC and MSKCC models are reported to be highly concordant, with 83% of patients classified into the same risk group by each model.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo cohort-based partitioned survival model in Microsoft Excel to compare the cost-effectiveness of NIVO+IPI versus sunitinib or pazopanib for the treatment of advanced RCC in intermediate/poor risk patients in the first-line setting. The model comprised six health states: (1) PFS on first-line treatment (2) PFS off first-line treatment (3) post-progression survival on first-line treatment (4) post-progression survival off first-line treatment (5) terminal care and (6) death. All patients entered the model progression-free and on first-line treatment. Variants of this model structure have been used in the modelling of treatment for patients with advanced RCC in previous NICE STAs. The model time horizon was set to 40 years with a 1-week cycle length. The primary outcome of the model was cost per additional QALY gained.

Time to event estimates were based on data collected from the CheckMate 214 trial for treatment with NIVO+IPI and treatment with sunitinib. OS and PFS estimates for treatment with pazopanib were assumed to be the same as treatment with sunitinib based on the outcomes from the COMPARZ trial. Time to treatment discontinuation (TTD) data for

pazopanib was assumed to be a proportion of TTD for sunitinib, based on the ratio of median TTD (0.95) in the COMPARZ trial. Utility estimates for patients receiving first-line treatment were derived from EQ-5D-3L data collected in the CheckMate 214 trial as a function of treatment arm (NIVO+IPI or sunitinib) and treatment status (on or off first-line treatment). Utility estimates for patients receiving second-line treatment were derived from a phase III randomised, open-label study of nivolumab versus everolimus in patients with previously treated advanced RCC (the CheckMate 025 trial). Utility values for patients treated with pazopanib were assumed to be the same as those treated with sunitinib. Resource use estimates were obtained primarily from the CheckMate 214 trial and to a limited extent from a previous technology appraisal of nivolumab monotherapy for previously treated advanced RCC (TA417). Unit costs derived from standard published sources were applied to the resource use data. All costs were expressed in UK pounds sterling for the 2017 price year. Costs and outcomes were discounted at 3.5% as NICE recommends.

In the CS, the base case comparison of NIVO+IPI versus sunitinib resulted in an incremental cost effectiveness ratio (ICER) per QALY gained of £28,865, with NIVO+IPI being more expensive (+£50,500) and more effective (+3.51 life years and +1.75 QALYs) than sunitinib. The probabilistic ICER was £30,886 per QALY gained. The company carried out a range of deterministic sensitivity analyses. The most influential parameter was the duration of first-line treatment. NIVO+IPI was also expensive (+£50,423) and more effective (+3.51 life years and +1.75 QALYs) than pazopanib, resulting in an ICER of £28,819 per QALY gained. The probabilistic ICER per QALY gained was £30,820.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The company's model is generally well structured and correctly implemented. The company corrected an error in the calculation of treatment costs for NIVO+IPI after the model had been submitted. The ERG has made investigated six areas of the company's economic analysis: modelling of OS; modelling of PFS, modelling of TTD; utility values; the proportion of patients receiving subsequent treatments; and treatment administration costs.

The ERG considers there to be three main issues with the company's modelling of OS. First, the assumption of a long-term immunotherapeutic effect on survival, which the ERG does not consider to be supported by the existing evidence. Second, the modelling of a cohort of patients of whom a proportion are expected to benefit from a long-term immunotherapeutic effect, which does not represent a proportion of patients benefitting from treatment, but rather that all patients will benefit from treatment if they live beyond a certain point. This results in an implausible pattern of mortality rates. Third, the use of a log-logistic curve to model a cohort

of patients where no-one benefits from an immunotherapeutic effect, which leads to implausible mortality rates in the long term.

The immaturity of the OS data from the CheckMate 214 trial introduces considerable uncertainty into the modelling of OS in this appraisal and the ERG urges that long-term OS estimates should be treated with caution. The ERG has remodelled OS from the CheckMate 214 trial without the assumption of an extra long-term immunotherapeutic effect, as it considers the evidence for such an effect to be limited and not robust.

The company use of PFS data from the CheckMate 214 trial defined by the primary definition and assessed centrally results in potential bias due to informative censoring and to a possible overestimation of the PFS gain for treatment with NIVO+IPI versus treatment with sunitinib due to differences in IRRC- and investigator-assessed PFS. The ERG prefers investigator-assessed PFS for use in economic modelling, as it represents a better estimate of the health-state costs incurred by patients in the relevant trial. In the CheckMate 214 trial, median investigator-assessed PFS was lower than IRRC-assessed PFS, meaning that some patients would have been treated as if they had progressed, and incurred costs related to progressed disease, even though they were not considered to have progressed by IRRC assessment.

The company base case includes a 5-year stopping rule for treatment with NIVO+IPI. The ERG does not consider this assumption to be justifiable in the base case, given that the licence for nivolumab does not specify a treatment stopping rule. The ERG also notes that the company has not explicitly included any effect of a treatment stopping rule on OS or PFS.

The [redacted] models used by the company to estimate TTD in the base case are neither a good visual fit to the data from the CheckMate 214 trial, nor statistically the best-fitting models. The company chose the [redacted]. The statistically best-fitting models investigated by the company were spline models ([redacted] and 1-knot hazard for treatment with sunitinib). The company used the default positioning of the knots for the spline models, which resulted in well-fitting models with long-term decreasing hazards in the long-term. The ERG considers it likely that the company's spline models would have been able to marry the requirement for a statistically and visually well-fitting model [redacted] in the long-term if the knots had been positioned differently.

The company's estimates of utility values are based on analysis of EQ-5D responses from patients in the CheckMate 214 trial. The company concluded that utility values that differed by

treatment arm and treatment status were the most appropriate values to use in the model. This means that progression status is not taken into account in the model QALY calculation.

The company has assumed that subsequent treatment will be received by patients in the proportions estimated by clinical experts. These proportions do not match those received in the CheckMate 214 trial. The ERG considers it preferable to use treatment estimates from the same source as the time-to-event outcomes, as OS, PFS and TTD may be affected by the type and availability of subsequent therapies. The ERG has investigated the impact on the ICER per QALY gained of assuming that patients receive subsequent therapies in the proportions from the CheckMate 214 trial and notes that the company assumption is conservative. However, the ERG notes that OS, PFS and TTD that would be experienced in UK clinical practice may differ from that in the CheckMate 214 trial depending on the type and balance of subsequent treatments patients receive.

The company base case does not include an administration cost for treatment with sunitnib or treatment with pazopanib. The ERG does not consider this to be a plausible assumption and has investigated the impact on the ICER per QALY gained of including an administration cost for the comparator treatments.

1.7 Summary of company's case for End of Life criteria being met

The company states that evidence from two RCTs (CheckMate 214 and the COMPARZ trials) and four real-world studies indicate that around half of all intermediate/poor risk patients are unlikely to survive for more than 24 months when treated with VEGFR-TKI agents in the first-line setting. It is added that life expectancy can be as low as 6 months for poor risk patients and reported that median OS was 26 months in the intermediate/poor risk population of the CheckMate 214 trial. The gain in life expectancy (NIVO+IPI versus sunitinib) is reported to be "in the order of years, rather than months" based on its economic modelling.

1.8 ERG commentary on End-of-Life criteria

The ERG considers the published evidence shows poor risk patients meet the NICE End-of-Life criterion of life-expectancy <24 months (all six studies report median OS <11 months for this subgroup). However, it is uncertain from the evidence presented whether intermediate risk patients meet this criterion (from five studies, median OS varied from 14.6 to 28.5 months with the median [redacted] in the CheckMate 214 trial). The CheckMate 214 trial is the only source of OS evidence for the combined intermediate/poor risk population. The evidence does not support life-expectancy <24 months whether considering median OS ([redacted]) or mean OS ([redacted]).

It is important to note, however, that there were 3.7 times as many patients with intermediate risk status than poor risk status in the CheckMate 214 trial. The ratio of intermediate risk to poor risk patients seen in clinical practice may be smaller (based on clinical opinion received by the ERG and on data from two large population studies, this ratio may be between 1.7 and 2.5). If so, the CheckMate 214 trial may be overestimating life expectancy for the intermediate/poor risk group as a whole given the differences in expected life expectancy reported for the subgroups individually.

The estimated mean extension to life based on economic modelling by the ERG is 26.6 months. Therefore the ERG concurs that the gain in OS for intermediate/poor risk patients exceeds 3 months.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the clinical effectiveness analysis. The ERG's requests for additional information were addressed to a good standard.
- Direct evidence has been presented for NIVO+IPI versus a relevant comparator (sunitinib) in the Checkmate 214 trial. The patient population in the CheckMate 214 trial appears to be broadly similar to the patient population that would be treated in NHS clinical practice, with a few notable exceptions highlighted in Section 1.9.2. Direct evidence demonstrates NIVO+IPI to have superior OS and ORR versus sunitinib.
- The ERG considers that the CheckMate 214 trial was generally well designed and well conducted and has a low risk of bias for most domains.
- Indirect evidence has been presented comparing NIVO+IPI versus the other relevant comparator (pazopanib) utilising data from the Checkmate 214 and COMPARZ trials. The COMPARZ trial appears to include a population of patients with similar characteristics to those in the CheckMate 214 trial. Indirect evidence demonstrates NIVO+IPI to have superior OS versus pazopanib.
- The ERG considers that the COMPARZ trial was generally well designed and well conducted and has a low risk of bias for most domains.

Cost effectiveness evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the base case analysis. The ERG's requests for additional information were addressed to a good standard.
- Variant of the model structure has been used in the modelling of similar treatments in a previous NICE STA.
- The decision model submitted by the company is generally implemented to a satisfactory standard.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- While the patient population in the CheckMate 214 and COMPARZ trials appear to be broadly similar to the patient population that would be treated in NHS clinical practice, it should be recognised that patients tended to be younger, all had clear-cell disease and a higher proportion had prior nephrectomy than would be seen in NHS clinical practice. The extent of the benefit for NIVO+IPI versus sunitinib for older patients, patients with non-clear cell RCC and patients who have not had prior nephrectomy is therefore unknown.
- Given the immaturity of the OS data, it is unknown whether the relative OS benefit for NIVO+IPI versus sunitinib observed at the first interim analysis of OS in the CheckMate 214 trial will be observed in the longer-term.
- There is uncertainty to what extent subsequent treatments received in the CheckMate 214 trial on disease progression impacted upon OS in both arms of the trial. Given also the differences in what patients received in this trial and what clinicians expect patients to receive in clinical practice, there is also uncertainty as to whether OS results reported in the trial would be replicated in clinical practice.
- It is unclear if the End-of-Life criterion that patients should have a short life expectancy, normally less than 24 months, has been met in the intermediate or intermediate/poor risk populations.
- In order to conduct the indirect comparison of NIVO+IPI versus pazopanib for PFS, it was necessary to use data for the intermediate risk group in the COMPARZ trial (pazopanib versus sunitinib) as PFS data were not available for the intermediate/poor risk group in this trial.
- A comparison of safety data between NIVO+IPI and pazopanib has not been presented.
- The wording of the marketing indications for all currently available and suitable treatments for second-line treatment options all specify that patients must have been previously treated with VEGFR-TKI (such as sunitinib or pazopanib) or cytokine agent (such as high-dose interleukin-2). Therefore, if NIVO+IPI were recommended and the marketing indications of the currently recommended drugs were strictly adhered to, then no treatment would be available to patients who did not respond to treatment with NIVO+IPI.

Cost effectiveness evidence

- There is uncertainty around the existence and form of any long-term immunotherapeutic effect on survival, as the evidence for a long-term immunotherapeutic effect on survival
- The modelling of OS for a cohort of patients of which a proportion are expected to achieve a long-term immunotherapeutic survival benefit results in an implausible pattern of mortality rates. This pattern of mortality rates occurs because all patients are modelled to return to general mortality risk after around 7 years of beginning treatment
- The modelling of OS for a cohort of patients of which none are expected to achieve a long-term immunotherapeutic survival benefit results in mortality rates falling below general mortality rates after around 20 years, which the ERG considers to be implausible
- The company uses IRRC-assessed PFS as the basis for its modelling of PFS, which results in higher PFS and PFS gain than investigator-assessed PFS. The ERG prefers

to use investigator-assessed PFS in cost effectiveness modelling if there is a difference between the results of the two tumour assessments, as investigator-assessed PFS should better reflect the treatment patients received during the trial and therefore the costs incurred as a result of their health state

- The company uses the primary definition of PFS as the basis for its modelling of PFS, which the ERG considers may introduce bias due to informative censoring
- The company base case includes a 5-year treatment stopping rule for NIVO+IPI, which is not a feature of the licence for nivolumab. The company has not taken into account any potential effect of a stopping rule in its modelling of OS and PFS
- The company's modelling of TTD does not represent a good statistical or visual fit to the K-M data from the CheckMate 214 trial
- Utility values in the first-line setting are applied according to treatment and treatment status (NIVO+IPI or sunitninb/pazopanib, on or off treatment), whereas the ERG would have also preferred to see investigation of the effect of health state on utility values
- The proportion of subsequent treatments received by patients in the company model are based on clinical advice to the company, which differs from the proportions received in the CheckMate 214 trial. Given that subsequent treatment may affect OS and PFS outcomes as well as cost, the ERG considers this to be an area of uncertainty
- Administration costs have not been included for treatment with sunitnib or treatment with pazopanib.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.11 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has explored the K-M data from the CheckMate 214 trial by intermediate- and poor-risk group separately. The ERG considers there to be some evidence that time-to-event outcomes may be different in the two risk groups, which may affect long-term trends for the combined intermediate/poor risk group. However, the ERG considers the data for the immediate risk and poor risk groups considered separately to be too immature as a foundation for robust long-term estimates. The ERG has therefore revised the company's modelling based on K-M data for the combined intermediate/poor risk group from the CheckMate 214 trial.

The ERG advocates the use of K-M data as far as possible when time-to-event evidence comes from a single trial, as the K-M data represent the best possible evidence for the patients in that trial until the time of the data cut. Parameter estimation is then restricted to any long-term trend evident in the tail of the K-M data. This approach avoids undue influence on the long-term extrapolation from protocol-induced features of the data or factors such as time to response, which occurs when using a fully parametric curve. The ERG has used this approach to modelling time-to-event data when providing alternative OS, PFS and TTD estimates.

The ERG's exploratory analyses include:

- remodelling OS using K-M data with a parametric tail. This analysis does not include the addition of an extra immunotherapeutic effect
- remodelling PFS using the investigator-assessed, secondary definition of PFS using a combination of K-M data and parametric curves
- remodelling TTD using K-M data with a parametric tail. This analysis does not included a 5-year treatment stopping rule for NIVO+IPI
- adding a utility effect for progression status based on the results of the company's existing analysis of the EQ-5D responses form the CheckMate 214 trial
- using the proportions of subsequent treatments from the CheckMate 214 trial rather than clinical advice to the company
- adding treatment administration costs for treatment with sunitnib and treatment with pazopanib.

The three ERG base case revisions that have the largest individual impacts on the ICERs per QALY gained for both the comparison of treatment with NVIO+IPI versus treatment with sunitinib and versus treatment with pazopanib are: ERG modelling of OS (increases the ICERs per QALY gained); ERG modelling of TTD (increases the ICERs per QALY gained); and addition of treatment administration costs for the comparators (decreases the ICERs per QALY gained).

1.12 Cost effectiveness conclusions

The ERG's revised base case yields an ICER of £38,152 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with sunitinib, which is £10,083 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are lower -£775) than those generated by the company for this comparison and incremental benefits that are lower (-0.49 QALYs) than those generated by the company.

The ERG's revised base case yields an ICER of £36,738 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with pazopanib, which is £8,716 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are lower -£2,490) than those generated by the company for this comparison and incremental benefits that are lower (-0.49 QALYs) than those generated by the company.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description presents an accurate summary of the underlying health problem. Key points made by the company and considered by the ERG to be of particular relevance for the current appraisal are presented in Box 1. Of note, in the CS, the company describes the underlying health problem in relation to advanced renal cell carcinoma (RCC) and metastatic RCC. In this ERG report we use the term advanced RCC to encompass patients not amenable to curative surgery or radiation and patients with metastatic RCC.

Box 1 Key points from the company's description of underlying health problem

Description of disease including prognosis and epidemiology

- Kidney cancer is the seventh most common cancer in the UK, but it is still relatively rare, accounting for only 3% of all new cancer cases in 2014.[1]
- Renal cell carcinoma (RCC), where cancerous cells develop within the epithelia of the renal tubules, is the most common type of kidney cancer, responsible for approximately 80% of all cases of kidney cancer diagnosed in the UK.[2,3]
- Over half of all kidney cancer cases are diagnosed in people aged 70 and over, with men up to twice as likely to develop RCC than women.
- Metastatic disease (Stage IV) is found in 30% of all patients at diagnosis[4-8] with around 75% of renal cancer being of the clear-cell histology.[9]
- Metastatic RCC is a life-threatening condition with a 5-year survival rate of only 10–15%.[10]

Burden of disease

- Detection of suspected RCC is often incidental as the disease can be relatively asymptomatic in the early stages.[11]
- Patients that do have symptoms usually present with pain or discomfort in the upper abdomen or back (flank pain), gross haematuria and a palpable lump or mass in the kidney area; these make up the classic triad of kidney cancer symptoms.[2,11]
- The altered immune response caused by the tumour may also result in symptoms such as hypercalcaemia, fever and weight loss.[2,11]
- Patients with metastatic disease may experience further physical symptoms based on the location of their metastases.
- The symptoms of advanced disease coupled with the psychological impact of suffering from a life-threatening disease can significantly impact individual patients' everyday lives and overall well-being.[12-15]
- Advanced RCC impacts on all domains of patient health-related quality of life (HRQoL) including physical and psychosocial function.[13]
- Importantly, treatment-related adverse events (TRAEs) from systemic therapies used in the management plan can further reduce HRQoL.[12,13]
- In addition to patient burden, advanced RCC can also present a 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.[13,16-18]

Source: adapted from CS, Section A1 and Section B1.3

2.2 Intermediate and poor risk disease

As the company highlight, multiple models are available to characterise prognosis [or risk] in RCC. Two of the most commonly used in advanced RCC are the Memorial Sloan Kettering

Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC), each of which categorises patients as favourable, intermediate or poor risk based on how many adverse prognostic factors are present.[19,20]

2.3 Company's overview of current service provision and the technology being appraised (NIVO+IPI)

The company's overview of current service provision is presented in Section B1.3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights the key points made by the company in Box 2. Most importantly, it should be noted that nivolumab in combination with ipilimumab (NIVO+IPI) is being proposed only for patients with intermediate **or** poor risk (hereafter referred to as intermediate/poor risk) advanced RCC, in line with its expected marketing indication (and NICE scope), see also Section 3 of this ERG report.

Box 2 Key points from the company's overview of current service provision

- Standard first-line management in the NHS is currently restricted to systemic vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine-kinase inhibitor (TKI) agents that have no proven significant benefit on overall survival (OS) and can be associated with significant toxicity.[21-24]
- Although interferon alpha (IFN-α) and high-dose interleukin-2 (IL-2) are alternative treatment options, these are used in very few, very select patients due to significant toxicities. Indeed, clinical consultation confirmed that no-one in the UK is currently treated with IFN-α and that only around 1% of treated metastatic RCC (mRCC) patients in the UK currently receive IL-2 in a single cancer centre. It is used either pre- or post-first-line VEGFR-TKI therapy for highly selected patients.[25]
- Nivolumab + ipilimumab (NIVO+IPI) is [anticipated to be] the first immunotherapeutic agent licensed for use in first-line advanced RCC and represents a 'step-change' in the management of this disease, building upon the value of nivolumab monotherapy in the second-line RCC setting.
- European Association of Urology (EAU) guidelines for the treatment of first-line metastatic RCC have been updated and now recommend NIVO+IPI as the standard of care in intermediate/poor risk patients with alternative agents (including sunitinib and pazopanib) being considered when NIVO+IPI is not safe or feasible.[26]

Source: adapted from CS, Section B1.3

Regarding systemic vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine-kinase inhibitor (TKI) agents, currently, the first-line treatment options for patients in NHS clinical practice are sunitinib or pazopanib. Bristol-Myers Squibb (BMS) market data to June 2016 and clinical opinion to the company suggest that approximately 60% of NHS patients receive pazopanib and approximately 40% receive sunitinib.[27] It was reported in the COMPARZ trial published in 2013 by Motzer et al[5] that pazopanib was non-inferior to sunitinib in terms of progression-free survival (PFS). A higher overall response rate (ORR) was reported with pazopanib compared to sunitinib (31% versus 25%) and it was reported in the COMPARZ trial that, in general, pazopanib was less toxic than sunitinib. Clinical advice to the ERG is that pazopanib is indeed considered by many clinicians to be less toxic than sunitinib. However, there is a 2-week break in treatment with sunitinib (after 4 weeks on treatment) and for this reason some patients may prefer sunitinib to pazopanib. The ERG also notes the results from

the blinded PISCES study[28] in which 169 patients were randomised to either sunitinib (4 weeks of daily sunitinib, 2 weeks of daily placebo, 4 weeks of daily sunitinib) or pazopanib (continuous daily use for 10 weeks) and then crossed over to the other treatment after a washout period. The authors concluded that 70% of patients preferred pazopanib, 22% preferred sunitinib and 8% expressed no preference. Physician preferences were consistent with patient preferences. More physicians preferred to continue their patients on pazopanib (61%) than on sunitinib (22%), with 17% stating no preference.

In addition to the treatment options highlighted in Box 2, the ERG notes that two other systemic VEGFR-TKI agents may soon be considered as first-line treatment options in NHS clinical practice. Soon after the company presented its submission to NICE, tivozanib was recommended as a first-line treatment option for patients with advanced RCC by NICE (for all risk patients).[29] Cabozantinib is also currently being considered by NICE as a first-line treatment option for patients with advanced RCC.[30] Similar to NIVO+IPI, cabozantinib is being considered only for patients with intermediate/poor risk disease.

Interferon alpha (IFN-α) and high-dose interleukin-2 (IL-2) are cytokine immunotherapy treatments requiring patients to be treated as inpatients.[31,32] The ERG notes that, since VEGFR-TKI agents became available, cytokines are rarely used in NHS clinical practice. Clinical advice to the ERG is that IFN-α is probably never used whereas high-dose IL-2 is reserved for a select group of patients (patients who are relatively young and who have favourable risk disease). It is rarely used because of the toxicity and relatively low response rates associated with this treatment, compared with VEGFR-TKI agents. For example, patients treated with IL-2 may experience a flu-like syndrome and experience substantial Grade 3 or Grade 4 toxicity, although adverse events (AEs) can be monitored and controlled in an inpatient setting and tend to be largely reversible.[31] The main attraction of IL-2 is that, while response to treatment is relatively low, patients with a complete response are considered to be effectively cured of RCC. Evidence from observational studies have reported ORRs of between 14%[33] and 17%[34] (with complete responses of between 5%[33] and 7%[34]). Ongoing responses to treatment are reported to be durable, with a median of 9.3 years and 10.1 years follow-up with high-dose and low-dose IL-2 respectively in one RCT.[35]

The company highlights that NIVO+IPI is an innovative type of immunotherapeutic treatment. Nivolumab and ipilimumab act as checkpoint inhibitors of programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), respectively, at their distinct yet complementary positions within the T-cell response pathway. They therefore have different mechanisms of action to the cytokines. If licensed, NIVO+IPI will be the first immunotherapeutic treatment option licensed for use in first-line metastatic RCC (for

intermediate/poor risk patients, only). A summary of other statements made by the company to support the innovative nature of NIVO+IPI is presented in Box 3.

The company considers that, for a proportion of patients treated with nivolumab monotherapy (and therefore NIVO+IPI), a long-term durable response will be achieved, lasting for years. As already noted, a similar effect has been observed for some patients treated with high-dose IL-2. Nivolumab is, however, a relatively new drug for patients treated with RCC, being recommended by NICE as a second-line monotherapy treatment option, in November 2016;[36] long-term data beyond 5 years are therefore currently lacking for this population (CS, Section B.2.13, Table 18). The company considers that an 'immunotherapeutic effect' has been observed in some patients treated with either nivolumab or ipilimumab monotherapies for melanoma (CS, Section B.3.3.2). The immunotherapeutic effect of NIVO+IPI is considered in relation to the evidence presented by the company to support the cost effectiveness of NIVO+IPO by the ERG in Section 5.4.3 of this ERG report.

Box 3 The innovative nature of NIVO+IPI

- NIVO+IPI was awarded a Promising Innovative Medicine designation in September 2017.
- This combination builds upon the value of nivolumab in the second-line RCC setting, which was the first targeted immunotherapy in advanced RCC to demonstrate proven survival benefit, significant clinical response and improved HRQoL.
- As the RCC landscape expands, treatment sequencing will become ever more important; with the introduction of NIVO+IPI in the first-line setting, patients will gain unprecedented advantages as they are able to achieve an immunotherapeutic effect earlier in their treatment pathway.
- Furthermore, the immunotherapeutic effect of NIVO+IPI offers an alternative safety profile to sunitinib that is manageable and familiar to clinicians already accustomed to using nivolumab treatment in the second-line setting.
- Indeed, the introduction of NIVO+IPI would change the treatment paradigm for such patients and thus represents a 'step-change' in the management of this condition.

HRQoL=health-related quality of life; NIVO+IPI=nivolumab in combination with ipilimumab; RCC=renal cell carcinoma
Source: adapted from CS, Section B2.12

The ERG agrees with the company's final statement reproduced in Box 3 that, if NIVO+IPI is recommended, access to this treatment may indeed change the treatment paradigm for advanced RCC, primarily by changing the current treatment pathway. Current second-line options include axitinib, nivolumab monotherapy, everolimus, cabozantinib and lenvatinib in combination with everolimus (Table 1). None of these treatment options are specific only to patients with intermediate/poor risk disease.

Table 1 Treatment options recommended by NICE for treating advanced RCC in NHS clinical practice (any line of treatment), as at the time of the CS (5 February 2018)

Agent	Marketing indication (in relation to RCC)*	NICE guidance (in relation to RCC)†
Sunitinib (Sutent)	SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.	**TA169 (25 March 2009):** Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
Pazopanib (Votrient)	Votrient is indicated in adults for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.	**First-line, TA215 (23 February 2011):** Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme. **Second-line, ID70 (2010):** No guidance issued (topic discontinued 14 April 2010).
Axitinib (Inlyta)	Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.	**TA333 (25 February 2015):** Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.
Nivolumab (Opdivo)	OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.	**TA417 (23 November 2016):** Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults, when the company provides nivolumab in line with the commercial access agreement with NHS England.
Everolimus (Afinitor)	Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.	**TA432 (22 February 2017):** Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy, only if the company provides it with the discount agreed in the patient access scheme.
Cabozantinib (Cabometyx)	CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.	**TA463 (9 August 2017):** Cabozantinib is recommended, within its marketing authorisation, as an option for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy, only if the company provides cabozantinib with the discount agreed in the patient access scheme.
Lenvatinib (Kisplyx) plus everolimus	Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF) -targeted therapy	**TA498 (24 January 2018):** Lenvatinib plus everolimus is recommended as an option for treating advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy, only if: their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1 and the company provides lenvatinib with the discount agreed in the patient access scheme.

Sources: *Marketing indications taken from the summary of product characteristics documents available on the European Medicines Agency website[37-43] and †NICE recommendations taken from the guidance available on the NICE website[36,44-49]

The company consider (CS, Section B.1.3, p14) that, "after first-line treatment with NIVO+IPI, it is anticipated that patients will go on to receive either cabozantinib or axitinib in the second-line setting, although some clinicians may want to consider sunitinib or pazopanib after first-line NIVO+IPI, if permitted by NICE to do so.[25]" Clinical advice to the ERG is that since the results of the METEOR trial[50] have shown everolimus to be inferior to cabozantinib in terms of overall survival (OS), PFS and ORR, everolimus is not commonly used in the second-line setting. Lenvatinib in combination with everolimus was only recommended by NICE in guidance published 24th January 2018. It has therefore only recently become a treatment option for NHS patients with advanced RCC in NHS clinical practice. Clinical advice to the ERG is that this combination is unlikely to be preferred to cabozantinib or axitinib due to evidence derived from a Phase II study[51] showing increased toxicity with lenvatinib.

The ERG highlights that, if the marketing indications of the currently recommended drugs were strictly adhered to (i.e. not used off-label), then no treatment would be available to patients who did not respond to treatment with NIVO+IPI. This is because both the marketing indications and NICE recommendations specify the type of treatment that is permitted first-line, none of which specify NIVO+IPI or indeed, any immunotherapy other than the now rarely used cytokines (see Table 1 of this ERG report). If NIVO+IPI were to become available as a first-line treatment option, nivolumab monotherapy would not be used for patients previously treated with NIVO+IPI.

Therefore, while the current wording of the marketing indications (and therefore NICE guidance) may be problematic, the company and the ERG both consider that if NIVO+IPI were to become available as a first-line treatment option, cabozantinib and axitinib are the most likely subsequent treatment options. Clinical advice received by the company is that cabozantinib may be more efficacious than axitinib but may also be associated with greater toxicity.[27] Clinical advice to the ERG is in broad agreement with that received by the company but it is noted that cabozantinib and axitinib have not been compared directly to one another.

A final key point to note is that the majority of recent trials of advanced RCC have also only included patients with a clear-cell histology, including all of the pivotal trials for the treatments recommended by NICE in Table 1.[22,51-57] Approximately 75% of patients with RCC have clear-cell disease. It is now known that patients with a clear-cell histology respond to treatment in a different way when compared to those without a clear-cell component, non-clear cell RCC being a more aggressive disease.[58] A systematic review and meta-analysis published in 2015 concluded that systemic treatments tend to be significantly less effective for non-clear cell RCC, with lower response rates and worse OS and PFS when compared with clear-cell RCC.[59] Clinical advice to the ERG is that sunitinib is commonly used as a first-line treatment

for patients with non-clear cell RCC since clinical efficacy has been shown from a large post-marketing prospective single arm study.[60] Anecdotal evidence and evidence from other small retrospective studies including pazopanib in the first-line setting[61-64] and nivolumab monotherapy for treatment of refractory patients with RCC[65] suggest that these agents may also be suitable for many patients with non-clear cell RCC.

2.4 Number of patients eligible for treatment with NIVO+IPO

The number of estimated patients eligible for treatment with NIVO+IPI is presented in the company's resource impact document. The information is summarised by the ERG in Table 2. The company estimates the number of eligible patients will grow by 6% each year, rising to 1233 in year 2 (2019) and reaching 1468 by year 2021.

Table 2 Estimated numbers of patients potentially eligible for treatment with NIVO+IPI

Parameter	Number	Source
Incidence of kidney cancer, 2013	8505	ONS 2015[66]
Incidence of kidney cancer, 2018*	11,382	Projected from ONS 2015[66]
Patients with RCC (80%)	9106	CRUK 2015,[67] Sachdeva et al 2014[3]
Patients with advanced RCC (30%)	2732	Abe et al 2013,[6] Figlin et al 2012,[7] Lane et al 2014,[8] Motzer et al 2013,[5] Tripathi et al 2014[4]
Patients with clear-cell histology (75%)	2049	CRUK 2016,[9] Linehan et al 2014[68]
Intermediate/poor risk (76%)	1557	Escudier et al 2017[69]
Total eligible patients in 2018 (75%)	1163†	BMS advisory boards, June 2014,[70] January 2016[71]

BMS=Bristol-Myers Squibb; CRUK=Cancer Research UK, ONS=Office for National Statistics; RCC=renal cell carcinoma
* Through 2005 to 2013, the average annual increase in kidney cancer incidence was reported to be approximately 6%.[66] It was therefore assumed that the incidence increased by 6% each year from 2013 to 2018
†Calculated by the ERG following all the assumptions above to be 1168 but reported by the company to be 1163
Source: BMS resource impact document, Section 3, p5

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE and that addressed within the CS is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 3 Comparison between final scope issued by NICE and company's decision problem

Parameter	Specification in the final scope issued by NICE	Summary of a comparison between the decision problem stated in the NICE scope and addressed in the company submission
Intervention	Nivolumab in combination with ipilimumab	Identical to final scope
Population	People with untreated, intermediate or poor risk (as per International Metastatic Renal Cell Carcinoma Database Criteria), advanced or metastatic renal cell carcinoma	Identical to final scope
Comparator (s)	Pazopanib Sunitinib	Identical to final scope
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	Identical to final scope
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 (QALY) If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out 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	As per final scope, the cost effectiveness of treatments expressed as incremental cost per QALY gained over lifetime horizon, with costs considered from an NHS perspective
Subgroups	None specified	Identical to final scope but at the request of the ERG, some subgroup analyses for intermediate and poor risk groups were made available

Source: final scope issued by NICE and CS, adapted from Section B.1.1, Table 1

3.1 Intervention

A description of NIVO+IPI is presented in Section B.1.2, Table 2 of the CS. The draft summary of product characteristics (SmPC) is presented in Appendix C to the CS.

An application was filed on 7 November 2017 to the European Medicines Agency (EMA) to allow NIVO+IPI to be used for the treatment of untreated, advanced RCC in adults with intermediate/poor risk disease. Nivolumab monotherapy is currently licensed for the treatment of advanced RCC after prior therapy in adults. Nivolumab is also indicated as a treatment option for a number of other malignancies: melanoma, non-small cell lung cancer, classical Hodgkin lymphoma, squamous cell cancer of the head and neck and urothelial carcinoma. Ipilimumab monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma. The anticipated indication in relation to the current appraisal is: "for the treatment of adult patients with intermediate/poor risk advanced renal cell carcinoma" (CS, Section B.1.2, Table 2). The Committee for Medicinal Products for Human Use opinion, marketing authorisation and the European Public Assessment Report are all expected to be available in the second and third quarters of 2018.

The company states (CS, Section B.1.2, Table 2) that NIVO+IPI potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell); this results in destruction of the tumour through pre-existing, intrinsic processes. Both nivolumab and ipilimumab are administered intravenously (IV). The dosage for the anticipated indication in relation to the current appraisal is based on the regimen used in the CheckMate 214 trial, i.e. nivolumab 3mg/kg administered IV over 60 minutes followed by ipilimumab at 1 mg/kg administered IV over 30 minutes, at least 30 minutes after the completion of the nivolumab infusion. Infusions were administered every 3 weeks for four cycles. Thereafter, nivolumab 3mg/kg was administered IV as a monotherapy over approximately 60 minutes every other week until treatment discontinuation.

3.2 Population

NIVO+IPI is intended for patients with advanced or metastatic (hereafter simply referred to as advanced) RCC. More specifically, it is intended for patients with previously untreated advanced RCC and who have intermediate/poor risk disease. Of note, however, while the evidence for NIVO+IPI is derived entirely from previously untreated patients, as noted by the company (CS, Section B.1.1), the anticipated license may not specify patients must be untreated.

As noted by the company and as previously highlighted in Section 2.2 of this ERG report, multiple models are available to characterise risk in RCC; two of the most commonly used

models are the Memorial Sloan Kettering Cancer Center (MSKCC)[19] and the International Metastatic RCC Database Consortium (IMDC).[20] Each of these models categorises patients as having favourable, intermediate or poor risk based on how many adverse prognostic factors are present. A comparison of the two models is presented in the CS (Section B.1.3, Table 3) where it is shown that the two models calculate risk using many of the same prognostic factors. Adverse prognostic factors in both models are considered by assessing time from diagnosis to systemic treatment, haemoglobin levels, calcium levels and Karnofsky performance status (KPS). In addition, the MSKCC includes levels of lactate dehydrogenase (LDH) as a prognostic risk factor whereas the IMDC considers absolute neutrophil count and platelet count as additional prognostic factors. For both scoring systems, a patient is considered to be at favourable risk if none of the adverse prognostic risk factors are present, at intermediate risk if less than three adverse prognostic risk factors are present and at poor risk if three or more adverse prognostic risk factors are present.

It is specified in the NICE scope that risk should be defined using the IMDC criteria. This is the model used in the CheckMate 214 trial from which the majority of evidence for NIVO+IPI is derived and the company states that this newer prognostic tool is believed to offer more granularity and is generally preferred by clinicians in the current era of targeted therapies. The ERG concurs with this statement. However, it should be noted that many previously published trials have used the MSKCC, including the previous CheckMate 016 trial of NIVO+IPI and a previous non-inferiority trial of pazopanib and sunitinib (the COMPARZ trial). The ERG notes that, in validating the IMDC, Heng et al 2013[72] reported that the IMDC and MSKCC model are highly concordant, with 83% of patients classified into the same risk group by each model.

3.3 Comparators

The comparators specified in the NICE scope and addressed by the company's decision problem are sunitinib and pazopanib. The recommended dose of sunitinib is 50mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks. The recommended oral dose of pazopanib is 800mg once daily, with no rest periods. NIVO+IPI has been compared with sunitinib in the CheckMate 214 trial. In order to compare NIVO+IPI with pazopanib, the company performed network meta-analyses. The ERG considered it would also be possible to compare NIVO+IPI with pazopanib via a simple indirect comparison and requested such an analysis from the company. For more information, see Section 4.7.2 of this ERG report.

As highlighted in Section 2.3 of this ERG report, these VEGFR-TKIs are the most commonly used first-line treatment options for advanced RCC. As also noted in Section 2.3, after the company presented its submission to NICE, tivozanib was recommended[29] and cabozantinib

is currently being considered as first-line treatment option by NICE.[30] The ERG considers sunitinib and pazopanib to be the most appropriate comparators in the current appraisal given these are the current standards of care.

3.4 Outcomes

Clinical evidence is reported in the CS for NIVO+IPO versus sunitinib for all five outcomes specified in the final scope: OS, PFS, response rates, AEs and health-related quality of life (HRQoL). Response rates are reported as ORR including complete and partial response along with the supporting outcomes of time to response (TTR) and duration of response (DoR). Comparative data for NIVO+IPI versus pazopanib are only reported for OS and PFS.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

No subgroups were specified in the final scope issued by NICE. No subgroup analyses were therefore presented for the cost effectiveness analysis. However, for the clinical effectiveness analysis, the CS does include results from some of the pre-specified subgroup analyses in the Checkmate 214 trial, namely results for patients with favourable risk status (despite this group of patients being outside the anticipated marketing indication for NIVO+IPI) and results by programmed death receptor ligand-1 (PD-L1) status.

During the clarification process, the ERG also requested that the company provide specific data for intermediate and poor risk groups separately. The rationale for the ERG's request is that, since risk is identified as a prognostic factor and median OS differs markedly by risk group (see Section 2.2 of this ERG report), it would be informative to consider the data for intermediate and poor risk groups separately. In particular, for considerations of clinical effectiveness, the ERG requested the data in relation to efficacy and subsequent treatments received. In terms of cost effectiveness, the ERG requested the data to allow exploration of the rationale for modelling intermediate/poor risk patients as a single subgroup.

The company provided the subgroup information requested by the ERG but with a number of concerns. These concerns are detailed in full in the company's clarification response and where relevant to the interpretation of the findings, summarised in Section 4.6.4 of this ERG report.

3.7 Other considerations

Both sunitinib and pazopanib are available to NHS patients only if the treatments are made available in accordance with the agreed arrangements of their respective Patient Access Schemes (PAS). For sunitinib this means offering the first cycle of treatment for free and for pazopanib this means offering the drug at a 12.5% discount off the list price. Nivolumab and ipilimumab are also currently only available to NHS patients if they are made available at discounted prices, in accordance with the agreed arrangements of their respective PAS arrangements (CS, Section B.3.7.1, p147). The details of these PAS arrangements are confidential. All the recommended second-line treatments are also only available via confidential PAS agreements. In this ERG report, no commercial price discounts for the second-line drugs are applied in the cost effectiveness analysis (this approach mirrors the company's approach in the CS).

As stated in Section B.1.4 of the CS, no equality considerations have been identified or are anticipated in relation to this appraisal.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the company's process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D to the CS.

4.1.1 Literature search methods

The company carried out a systematic search of the literature in May 2017 to identify RCTs investigating the efficacy and safety of NIVO+IPI and comparator studies for the treatment of people with previously untreated advanced RCC. The search terms were relevant and included medical subject headings and free-text terms as well as an RCT filter. The search was limited to English Language and human studies. The company searched the following databases: Medline, Medline in Process, Embase and The Cochrane Library (CENTRAL only). The company reported results from hand searches of the following conference sites: American Society of Clinical Oncology (ASCO), ASCO-Genitourinary (ASCO-GU), European Society for Medical Oncology (ESMO) and European Conference for Clinical Oncology (ECCO) and National Cancer Institute of Brazil (INCA). The company also reported searches of clinicaltrials.gov for relevant clinical trials.

The ERG considers that the company's searches were appropriate for the identification of key studies of treatments for RCC and were carried out to an adequate standard. The ERG also re-ran the search conducted by the company on 23 February 2018 and confirms that no relevant papers were missed from when the original search was run in May 2017. However, following the ERG's update, the ERG identified that the previously unpublished CheckMate 214 trial was published in a peer reviewed journal (21 March 2018).[73]

4.1.2 Eligibility criteria

The full eligibility criteria employed in the company's systematic review is presented in Appendix D to the CS, Table 4. In summary, eligible studies were required to be RCTs which included the population of interest (patients with previously untreated, advanced or metastatic RCC) and at least one of the efficacy or safety outcomes specified in the NICE scope (OS, PFS, ORR, frequency of AEs or discontinuation due to AEs). The ERG notes that HRQoL was not considered an outcome of interest for eligibility for the clinical effectiveness review. The company further notes that RCTs that investigated the clinical efficacy and/or safety of a broader range of potential interventions than those that are available within NHS England were eligible for inclusion. Overall, the ERG considers that the eligibility criteria applied are appropriate to the decision problem set out in the final scope issued by NICE.

Following accepted standards for conducting systematic reviews, the company states that the eligibility criteria were applied in two screening stages. Two reviewers independently inspected each reference (title and abstract) identified by the literature searches (initial screening). Relevant citations were obtained in full and independently assessed against the full eligibility criteria (secondary screening). In the event of disagreement between the two reviewers, a third reviewer independently assessed the paper and consensus was reached regarding eligibility.

4.1.3 Data extraction

After applying the eligibility criteria to the full-text papers, all the papers meeting the inclusion criteria were retained for data extraction. The ERG notes that the optimal approach to data extraction is dual data extraction. It is unclear if this approach was utilised for the systematic review of clinical effectiveness provided in the CS.

4.1.4 Quality assessment methods

The company carried out a risk of bias assessment for all of the RCTs included in their systematic review using the approach recommended by NICE.[74] It is, however, unclear to the ERG whether this assessment was completed by one reviewer, or independently by two reviewers. The latter method is considered to be the preferred method.

4.1.5 Data synthesis

The company identified 57 publications reporting on 46 unique trials. Only one trial, the Phase III CheckMate 214 trial, compared the intervention of interest (NIVO+IPI) with a comparator of interest (sunitinib). The trial and patient characteristics and findings of the CheckMate 214 trial were appropriately presented narratively in the CS. The other 45 trials were considered for inclusion in the company's network meta-analyses necessary to enable NIVO+IPI to be compared with the other comparator of interest (pazopanib), see Section 4.7 of this ERG report for more details.

4.1.6 Critique of the review methods

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be satisfactory.

4.2 Identified trials

4.2.1 Studies of NIVO+IPI

The CheckMate 214 trial was the only trial that compared NIVO+IPI with sunitinib. No trial was identified that compared NIVO+IPI with pazopanib.

Supportive evidence for NIVO+IPI was also presented in the CS from the Phase I CheckMate 016 trial;[75] this trial was not included in the company's systematic review. This trial included patients of all risk status and investigated various combinations of nivolumab-based therapy in patients with advanced RCC, including the anticipated licensed dose of NIVO+IPI for RCC and the dose that has been licensed for melanoma. The CheckMate 016 trial does not include any data on relevant comparators. Some information on this trial is provided in Appendix 5 of this ERG report (Section 9.5).

4.2.2 Studies of comparator treatments (sunitinib and pazopanib)

Aside from the CheckMate 214 trial, the company's systematic review included 45 other unique trials assessing a range of interventions for advanced RCC. Two of the included studies included a comparison of sunitinib and pazopanib (the COMPARZ trial and PISCES study). There were seven other trials of sunitinib[5,53,76-80] or pazopanib[22] in which these VEGFR-TKIs were compared with other first-line treatments. Three trials evaluated different ways of sequencing treatment with sunitinib[81,82] or pazopanib.[83] Three trials evaluated the effectiveness of sunitinib as adjuvant therapies;[84-86] all patients receiving adjuvant therapy had locally advanced disease and were considered to be at risk of recurrence. One other trial evaluated the efficacy and safety of sunitinib in combination with IFN-α.[87]

The CheckMate 214 trial and COMPARZ trials were included in the various NMAs conducted by the company. The company's NMAs also included nine other trials of sunitinib[53,76,78,79,82-85] or pazopanib[22] which were included in the company's systematic review and an additional trial (not included in the systematic review) that compared the efficacy and safety of sunitinib versus IFN-α.[56] Further information about the NMAs conducted by the company is provided in Section 4.7 of this ERG report.

4.3 Characteristics of CheckMate 214 trial

4.3.1 Trial characteristics

CheckMate 214 is an ongoing Phase III, randomised, open-label study of NIVO+IPI versus sunitinib in patients with previously untreated, advanced RCC with a clear-cell component. Key eligibility criteria are summarised in Table 4. Patients were randomised in a 1:1 ratio to receive treatment with NIVO+IPI or sunitinib. Randomisation was stratified by IMDC score (0 [favourable rosk] versus 1 or 2 [intermediate risk] versus 3 to 6 [poor risk]) and geographic region (United States versus Canada and Europe versus the rest of the world). From October 2014 through February 2016, 1096 patients were randomly assigned to treatment at 184 sites in 28 countries including six sites in the UK, of which four were in England. The ERG notes the number of sites is reported to be 175 in the published paper.

Table 4 Key eligibility criteria in the CheckMate 214 trial

Key inclusion criteria	Key exclusion criteria
• Previously untreated advanced RCC with a clear-cell component • Aged 18 years of age or older • Measurable disease according to RECIST, version 1.1 • Favourable, intermediate or poor risk disease as per the IMDC criteria (IMDC scores of 0, 1 or 2, 3 to 6, respectively) • Performance-status score of 70 or higher (on a scale from 0 to 100, with higher scores indicating lesser disability)	Central nervous system metastases or autoimmune disease and glucocorticoid or immunosuppressant use

IMDC=International Metastatic RCC Database Consortium; RCC=renal cell carcinoma; RECIST= Response Evaluation Criteria in Solid Tumors
Source: Motzer et al 2018

Although the trial included patients with favourable risk disease, the co-primary endpoints (OS, PFS and ORR) were analysed only in the combined intermediate/poor risk population (n=839), see also Section 4.5 of this ERG report. Therefore, the population of key interest in the CheckMate 214 trial was patients with intermediate/poor risk disease. As noted in Section 3.2 of this ERG report, it is this population with intermediate/poor risk disease that is of relevance to the current appraisal.

The ERG notes that, while pazopanib may be slightly more commonly used in clinical practice than sunitinib (see Section 2.3 of this ERG report), only sunitinib has been demonstrated to be superior to a previously used active agent in clinical practice (versus IFN-α);[56] pazopanib has only been demonstrated to be superior to best supportive care[22] (and non-inferior to sunitinib in the COMPARZ trial). Therefore, the ERG considers that sunitinib was the best choice of comparator in the CheckMate 214 trial.

Patients received treatment until disease progression or until unacceptable toxicity at the recommended doses of NIVO+IPI or sunitinib for advanced RCC as described in Sections 3.1 and 3.3 of this ERG report. Therefore, dose delays due to AEs were permitted in both arms but no dose increases/reductions were allowed in the nivolumab or ipilimumab arm, unlike in the sunitinib arm. Thus, dose escalations of sunitinib were permitted as per the approved product label when a concomitant CYP3A4 inducer was needed and a maximum of two sunitinib dose reductions in 12.5mg increments was allowed (CSR, Section 3.4.1).

Disease progression was assessed as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) criteria.[88] The ERG also notes that RECIST criteria were developed based on data from clinical trials of cytotoxic chemotherapy agents for advanced malignancies.[89] However, it has been documented, largely from trials of melanoma, that many of the newer immunotherapy drugs may lead to atypical patterns of response.[90-92] It has been observed (in typically 10% or less of patients[92]) that response may take longer with immunotherapy than with cytotoxic agents and hence initial imaging may suggest disease progression. Furthermore, for some patients, clinical response to immune therapies can occur even after progressive disease has been observed using RECIST criteria, a phenomenon commonly known as “pseudoprogression”. As a result, modified response criteria (based on World Health Organization criteria) known as the immune-related response criteria were proposed and published on 1 December 2009.[93] More recently, consensus guidelines[92] for using modified RECIST criteria (known as iRECIST) in trials were published on 2 March 2017. A comparison of the RECIST criteria with the immune-related response criteria and iRECIST criteria has been presented in Appendix 1, Section 9.1 to this ERG report.

The ERG notes that the authors of the iRECIST consensus guidelines[92] recommend RECIST v1.1 as the primary criteria for the design of Phase II and Phase III RCTs, the authors noting that, for non-immunotherapy treatments (such as VEGFR-TKIs), RECIST v1.1 and iRECIST should yield almost identical results. Therefore, the use of the RECIST v1.1 was appropriate for the CheckMate 214 trial. The authors of the iRECIST consensus guidelines[92] do however recommend the use of iRECIST for exploratory analyses. Since these consensus guidelines[92] were published after the database lock for the CheckMate 214 trial, it was not possible to use the iRECIST criteria for exploratory analyses in this trial.

In the CheckMate 214 trial, patients could, however, continue treatment beyond initial RECIST-defined progression if they were considered by the investigator to be experiencing clinical benefit and tolerating the study drug. Patients treated beyond initial RECIST-defined progression discontinued study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumour burden volume from time of initial progression

(including all target lesions and new measurable lesions) according to investigator assessment. Allowing treatment beyond RECIST-defined progression and confirming disease progression at the next assessment, as occurred in the CheckMate 214 trial, is consistent with recommendations in the iRECIST guidelines to allow for "pseudoprogression".

Of note, although the trial is ongoing, the data monitoring committee (DMC) recommended early termination of the trial for benefit when the planned first interim analysis for OS was conducted (7 August 2017). A November 2017 protocol amendment now permits crossover from the sunitinib arm to the NIVO+IPI arm but all data reported in the CS are from the first-interim analysis for OS (7 August 2017).

Overall, [redacted] patients received at least one infusion of NIVO+IPI ([redacted] of all randomised patients to the NIVO+IPI arm) and [redacted] patients received at least one dose of sunitinib ([redacted] of all randomised patients to the sunitinib arm). At the time of the database lock, the median duration of therapy was 7.9 months in the NIVO+IPI arm, with a median of [redacted] nivolumab doses and [redacted] ipilimumab doses received, and 7.8 months in the sunitinib group, with a mean daily dose of [redacted] mg/day. In the intermediate/poor risk group, [redacted] of all patients were still on treatment in the NIVO+IPI arm and [redacted] of all patients were still on treatment in the sunitinib arm. It is also reported that a further [redacted] of intermediate/poor risk patients in the NIVO+IPI arm and [redacted] of intermediate/poor risk patients in the sunitinib arm had received subsequent cancer therapy.

4.3.2 Baseline characteristics of patients enrolled in the CheckMate 214 trial

Data on patient characteristics reported in the CS (Table 6) and CSR (Table 3) show that baseline characteristics were well balanced between arms. Patient characteristics of those in the intermediate risk group were very similar to the all risk group enrolled into the trial, with the obvious exception of risk status. In the CheckMate 214 trial, there were 23% of patients with favourable risk disease, 61% with intermediate risk disease and 16% with poor risk disease. Clinical advice received by the ERG is that in clinical practice, there would be fewer patients with intermediate risk disease (approximately 50%) and more patients with poor risk disease (approximately 30%). Baseline characteristics of patients are summarised in Appendix 3, Section 9.3 of this ERG report (Table 41).

In summary, in the intermediate/poor risk group, most patients were white (87%), male (73%) with a median age of 62 years in the NIVO+IPI arm and 61 years in the sunitinib arm. Where recorded, most patients had PD-L1 tumour expression <1% (72%). Most patients also had good performance status (69% with a KPS score of 90 or 100) and intermediate risk disease (79%). Most patients (79%) had two or more sites of advanced disease, the most common

metastatic sites being the lung (69%) or and/or lymph node (48%). The majority of patients had had prior nephrectomy (90%) but few had had prior radiation therapy (12%) and less than 1% had received adjuvant or neoadjuvant systemic therapy.

Based on the characteristics presented, the ERG considers the patients in the trial are broadly similar to patients that would be treated in NHS clinical practice. It is, however, noted that the patients were younger than would be seen in clinical practice (a common issue with clinical trials) and there appears to be slightly more intermediate risk patients and slightly fewer poor risk patents than would be seen in clinical practice (See Section 6 for more information). In addition, clinical advice to the ERG is that the proportion of patients with prior nephrectomy in the trial (90%) may be slightly higher than the proportion for similar patients in NHS clinical practice (approximately 70%). Older patients, patients with clear cell disease, patients with poor risk disease and patients without nephrectomy are expected to have a worse prognosis than younger patients, patients with non-clear cell disease, intermediate risk disease and prior nephrectomy.

4.4 Risk of bias assessment for the CheckMate 214 trial

The company assessed the risk of bias of the CheckMate 214 trial using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[94] The ERG considers that the CheckMate 214 trial was generally well designed and well conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for most domains. While the open-label design provides the opportunity for subjective results and investigator-assessed outcomes to be biased, the co-primary outcomes of PFS and ORR were independent radiology review committee (IRRC)-assessed, conducted in a blinded manner. The other co-primary outcome of OS is an objective outcome that should not be prone to bias.

Table 5 Assessment of risk of bias for the CheckMate 214 trial

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree, the open-label nature of the trials provides an opportunity for subjective results and investigator-assessed outcomes to be biased
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree, the company made available the clinical study report, protocol and statistical analysis plan alongside its submission
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Agree
Were appropriate methods used to account for missing data (LOCF, MMRM)?	Yes	Agree

Source: CS, Table 8 and ERG comment

4.5 Statistical approach adopted for the CheckMate 214 trial

In this section, the ERG provides a description and critique of the statistical approaches used to analyse efficacy data collected during the CheckMate 214 trial that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR),[95] the trial protocol,[96] the trial statistical analysis plan (TSAP)[97] and the CS.

Outcomes analysed

There are three co-primary outcomes of the CheckMate 214 trial: IRRC-assessed PFS in intermediate/poor risk patients, OS in intermediate/poor risk patients, and IRRC-assessed ORR in intermediate/poor risk patients. Investigator-assessed PFS and investigator-assessed

ORR in intermediate/poor risk patients were also analysed. The definitions used and methods of analysis for the co-primary outcomes are provided in Table 6.

Table 6 Definitions and analysis methods of the co-primary outcomes of the CheckMate 214 trial

Outcome	Definition	Analysis method
PFS in intermediate/poor risk patients	*Primary definition (PFS censored at subsequent therapy):* • Defined as time between the date of randomisation and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Patients who died without a reported progression were considered to have progressed on the date of their death. • Patients were censored upon receiving subsequent therapy (censoring rules listed on page 24 of the CS) *Secondary definition (no censoring for subsequent therapy):* • Defined as above, but patients were not censored upon receiving subsequent therapy • Censoring rules listed on page 24 of the CS	PFS was estimated via the K-M product limit method. Two-sided 95% CI for the median PFS were computed for each randomised arm. HR and corresponding two-sided 99.1% CI were estimated using a Cox PH model, with treatment arm as a single covariate, stratified by the stratification factors
OS in intermediate/poor risk patients	Defined as the time from randomisation to the date of death from any cause	OS was estimated via the K-M product limit method. Two-sided 95% CI for the median OS were computed for each randomised arm. HR and corresponding two-sided 99.8% CI were estimated using a Cox PH model, with treatment arm as a single covariate, stratified by the stratification factors
ORR in intermediate/poor risk patients	Defined as the proportion of randomised patients who achieved a best response of complete or partial response based on IRRC assessment (as per RECIST v1.1)	Response rate was estimated by Clopper–Pearson method with a two-sided 95% CI

CI=confidence interval; HR=hazard ratio; IRRC=independent radiology review committee; K-M=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; RECIST=Response Evaluation Criteria in Solid Tumors
Source: CS, Table 5 and Table 7

As noted in Table 6, the company used two definitions of PFS: the primary definition, which included censoring for subsequent therapy, and the secondary definition, which did not include censoring for subsequent therapy. The ERG considers that censoring for the initiation of an effective anticancer treatment before progression occurs may be an example of informative censoring.[98] Patients in the CheckMate 214 trial may have been taken off their allocated study treatment before progression for reasons such as toxicity, patient or physician preference, initiation of non-protocol therapy, or inadequate response. If censored patients have a different risk of treatment failure to those who continue receiving study treatment, then one of the key assumptions of the Kaplan-Meier (K-M) method, called non-informative censoring, is violated. Consequently, PFS estimates obtained from the K-M method may be biased for the primary

definition of PFS. The ERG is of the opinion that censoring for subsequent therapy should have been conducted as part of a sensitivity analysis, rather than the primary analysis of PFS. The ERG considers that results from the analysis of PFS according to the secondary definition of PFS are likely to be less prone to bias than those from the analysis of PFS according to the primary definition.

The overall experiment-wise type 1 error rate (alpha) for the CheckMate 214 trial's co-primary outcomes is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS. A hierarchical testing procedure was used to preserve the type 1 error rate of 0.05. The endpoints of PFS, OS, and ORR were first analysed in intermediate/poor risk patients, and if statistically significant treatment effects were observed, these endpoints were then analysed in all randomised patients.

Safety data for all treated patients (who received any dose of study therapy) were presented as summaries of any Grade and Grade 3 to 4 AEs, serious adverse events (SAEs), treatment-related AEs (TRAEs), treatment-related SAEs (TRSAEs), treatment discontinuation due to AEs, immune-mediated AEs (IMAEs) and treatment-related deaths. HRQoL was assessed in all randomised patients by the Functional Assessment of Cancer Therapy-General (FACT-G) and (Functional Assessment of Cancer Therapy – Kidney Symptom Index) FKSI-19 questionnaires. Global health status was assessed by the EQ-5D-3L instrument.

The ERG notes that all outcomes were pre-specified in the TSAP, and all results are provided in the CSR.

Proportional hazards

The ERG notes that the Cox proportional hazards (PH) method was used to estimate the OS and PFS hazard ratios (HRs) for the CheckMate 214 trial. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time within each trial. From examining the K-M data provided to the ERG, the ERG considers that the PH assumption may be violated for OS, for IRRC-assessed PFS (primary and secondary definitions) and for investigator-assessed PFS (primary and secondary definitions) in the intermediate/poor risk population. Consequently, the ERG considers that the reported HRs for OS and PFS data from the CheckMate 214 trial should be interpreted with caution as HRs are not an appropriate summary of treatment effect when the PH assumption does not hold. It is not possible to know whether the reported HRs would overestimate or underestimate the effect of NIVO+IPI versus sunitinib. The methods and results of the ERG's testing of the PH assumption are provided in Appendix 2 in Section 9.2 of this ERG report.

Sample size calculation

The company calculated that for PFS, 583 events were required among the randomised intermediate/poor risk patients for a two-sided alpha=0.01 log-rank test to detect an HR of 0.73 for NIVO+IPI in comparison to sunitinib with at least 90% power. For OS, 639 events were required to provide 90% power to detect a HR of 0.766 with an overall type 1 error of 0.04 (two-sided). The ERG notes that ORR was added as a co-primary endpoint after the sample size calculation was specified in the SAP; the alpha split was consequently modified so that there was 0.009 to evaluate PFS, and there was 0.001 to evaluate ORR.

The company estimated that approximately 1070 patients would need to be randomised in a 1:1 ratio, including 820 intermediate/poor risk patients and 250 favourable risk patients. Assuming a 21% screen failure rate, the company planned to enroll approximately 1355 patients.

In the company's response to the ERG clarification letter, the company confirmed that, in June 2017, the analysis plan was revised to take into account the decreased rate at which IRRC-assessed PFS events were observed in the CheckMate 214 trial. The company estimated that 465 events were required to provide 80% power for the final analysis of PFS.

Interim analyses and termination of trial

Two interim analyses of OS were planned. The first-interim analysis of OS was planned at the time of the final ORR and PFS analysis. At this time, approximately 330 OS events (half of the targeted total OS events for final analysis) were expected, so an adjusted alpha of 0.002 was applied (to provide 99.8% CI). The stopping boundaries at the interim OS analyses were derived based on the number of deaths using the O'Brien and Fleming alpha-spending function.

Following the first-interim analysis of OS, the DMC recommended early termination of the trial for benefit since the pre-specified stopping boundary for OS was crossed. The ERG is aware that there is evidence that some trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time of stopping.[99-101] At the time of the first-interim analysis, deaths had occurred in 32.9% of NIVO+IPI patients and 44.5% of sunitinib patients. The ERG notes that in a previous appraisal of nivolumab (for previously treated locally advanced or metastatic squamous non-small cell lung cancer, TA483[102]), the CheckMate 017 trial was also stopped early for benefit on the recommendation of the DMC. In the CheckMate 017 trial, the 18-month (almost fully mature) efficacy data that subsequently became available appeared to support the DMC's decision to stop the trial early. Nonetheless, relative survival between the trial arms in the CheckMate 214 trial is based on immature data,

and so the ERG considers that it is unknown whether the OS benefit observed at the first-interim analysis of OS will be observed in the longer-term.

Protocol amendments

Protocol amendments and the rationale for amendments prior to the first-interim analysis for OS (7 August 2017, CSR, p22) are listed in the CSR (pp44-45). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the planned first-interim analysis of OS so amendments were unlikely to have been driven by the results of the trial.

Subgroup analyses

Subgroup analyses of each of the co-primary outcomes of the CheckMate 214 trial were pre-specified in the TSAP (pp35-36, p38). For the intermediate/poor risk group, these subgroup analyses were:

- Age (<65 versus ≥65 to <75 versus ≥75)
- Gender (male versus female)
- Race
- Region (US versus Canada/West Europe/North Europe versus Rest of the World)
- KPS(<90 versus ≥90)
- Baseline IMDC prognostic score (1-2, ≥3)
- Prior adjuvant or neo-adjuvant therapy for localized or locally advanced RCC (Yes, No)
- Prior nephrectomy (Yes, No)
- Prior radiotherapy (Yes, No)
- Time from initial disease diagnosis to randomization (<1 year, ≥1 year)
- Lactate dehydrogenase (LDH) level (≤1.5 x upper limit of normal (ULN), >1.5 x ULN)
- Haemoglobin (<lower limit of normal (LLN), ≥LLN)
- Corrected calcium (≤10 mg/dl, >10mg/dl)
- Alkaline phosphatase (<ULN, ≥ULN)
- Baseline PD-L1+ status based on a 1% cut off
- Baseline PD-L1+ status based on a 5% cut off
- Baseline PD-L1+ status based on a 10% cut off

Results of these pre-specified subgroup analyses are presented in the CSR (pp77-81, pp103-107, pp116-120). The company also pre-specified that exploratory analyses would also be performed for efficacy endpoints in the favourable risk patient subgroup. Results of these exploratory analyses are summarised in the CS (pp38-39) and are presented in full in the CSR (p75, p85, p87, p89, p92, p98, p101, p108, p113).

Furthermore, as part of the clarification process, the ERG requested that the company provide specific data from the CheckMate 214 trial for intermediate and poor risk patient subgroups separately, as discussed previously in Section 3.6 of this ERG report. These analyses are post-hoc subgroup analyses, and hence should be treated as exploratory analyses only.

4.6 Findings from the CheckMate 214 trial

Results from the CheckMate 214 trial are presented in the CS from the planned first-interim analysis for OS (7 August 2017). Median patient follow-up at this time was 25.2 months and the minimum follow-up was 17.5 months.

4.6.1 Overall survival in intermediate/poor risk patients

At the time of the data cut-off date, deaths had occurred in 140 patients (32.9%) in the NIVO+IPI arm and in 188 patients (44.5%) in the sunitinib arm. Median OS was not reached (95% confidence interval [CI]: 28.2 to not evaluable [NE]) in the NIVO+IPI arm and was 26.0 months (95% CI: 22.1 to NE) in the sunitinib arm. The HR for OS demonstrated a statistically significant treatment effect for NIVO+IPI in comparison to sunitinib (HR=0.63, 99.8% CI: 0.44 to 0.89; p<0.001).

The company provided a K-M curve for OS, which is presented in Figure 3 of the CS. The 6-month OS rate was [redacted] and [redacted] in the NIVO+IPI and sunitinib arms, respectively, and the 12-month rate was [redacted] and [redacted], respectively. The 18-month OS rate was [redacted] and [redacted] in the NIVO+IPI and sunitinib arms, respectively, and the 24-month rate was [redacted] and [redacted], respectively.

The ERG notes that subsequent therapy received following disease progression may impact on OS. It is however noticeable that [redacted] patients received subsequent therapy in the NIVO+IPI arm ([redacted]) than in the sunitinib arm ([redacted]). While [redacted] received subsequent radiotherapy ([redacted] in the NIVO+IPI arm and [redacted] in the sunitinib arm) or surgery ([redacted] and [redacted] respectively), [redacted] patients in the NIVO+IPI arm received subsequent systemic therapy ([redacted] versus [redacted]) including chemotherapy ([redacted] versus [redacted]). Of note, [redacted] of patients in the sunitinib arm received subsequent nivolumab (compared to [redacted] in the NIVO+IPI arm). Other subsequent systemic therapies included sunitinib, pazopanib, carbozantinib, axitinib and everolimus (See Section 5.2.9, ***[redacted]22 of this ERG report for further details about the receipt of these subsequent therapies). As noted in Section 2.3, based on clinical advice to the company and ERG, it is expected that if recommended as a first-line treatment, nearly all patients treated with NIVO+IPI would receive carbozantinib or axitinib on disease progression. The company also considers that most patients treated with first-line sunitinib would receive nivolumab on disease progression (60%); the ERG agrees that

nivolumab would usually be the second-line treatment option of choice for patients not previously treated with NIVO+IPI. However, in the CheckMate 214 trial, [redacted] of patients in the NIVO+IPI arm received subsequent carbozantinib/axitinib and [redacted] in the sunitinib arm received subsequent nivolumab. There is, therefore, uncertainty to what extent the treatments received in the trial impacted upon OS. There is also uncertainty as to how similar OS reported in the trial would be to OS observed in clinical practice, given differences in what patients actually received and what clinicians would prefer.

4.6.2 Progression-free survival in intermediate/poor risk patients

Primary definition (censoring for subsequent therapy)

For IRRC-assessed PFS with censoring for subsequent therapy (primary definition), a total of [redacted] and [redacted] of patients in the NIVO+IPI and sunitinib arms were censored, respectively. The most common reason for censoring was subsequent therapy; [redacted] of NIVO+IPI patients and [redacted] of sunitinib patients received subsequent therapy prior to disease progression.

Median PFS (primary definition) was 11.6 months (95% CI: 8.8 to 15.5) in the NIVO+IPI arm and 8.4 months (95% CI: 7.0 to 10.8) in the sunitinib arm. The corresponding HR was not statistically significant (HR=0.82, 99.1% CI: 0.64 to 1.05), but was described by the company as being clinically meaningful.

The company states that results for investigator-assessed PFS (primary definition) were concordant with the results for PFS as assessed by IRRC. Median investigator-assessed PFS (primary definition) was [redacted] months for NIVO+IPI patients and [redacted] months for sunitinib patients, with a HR of [redacted]. The ERG notes that although the HRs for investigator-assessed PFS and IRRC-assessed PFS are [redacted], there are [redacted]. Median PFS is estimated to be [redacted] for NIVO+IPI patients when assessed by IRRC in comparison to assessment by the investigator.

Secondary definition (no censoring for subsequent therapy)

A total of [redacted]% and [redacted]% of subjects in the NIVO+IPI and sunitinib arms, respectively, were censored. Median PFS (secondary definition) was [redacted] months (95% CI: [redacted]) in the NIVO+IPI arm and [redacted] months (95% CI: [redacted]) in the sunitinib arm, resulting in a HR of [redacted] (99.1% CI: [redacted]; [redacted]. The results were therefore similar to the results for IRRC-assessed PFS in which patients were censored for subsequent therapy (primary definition). The HR for investigator-assessed PFS (secondary definition) (HR=[redacted]) was [redacted]. Median PFS was not reported for investigator-assessed PFS (secondary definition).

ERG comment on PFS results

The fact that analyses of both IRRC-assessed PFS (primary definition) and investigator-assessed PFS (primary definition) [redacted], provides further evidence that the assumption of PH is violated for the IRRC-assessed PFS and/or investigator-assessed PFS (See also Section 4.5 of this ERG report). The reason for the [redacted] in the NIVO+IPI arm by IRRC-assessment and investigator assessment is unknown. However, as noted in Section 4.3.1 of this ERG report, response may take longer with immunotherapy than with cytotoxic agents and hence initial imaging may suggest disease progression. It is likely that investigators were more conservative in determining disease progression in order to enable the patient to move to a different treatment.

The ERG also notes that PFS according to the secondary definition was not taken into consideration in the splitting of alpha for the study. Hence, alongside the identified issues with the PH assumption, the [redacted]

Nonetheless, the ERG still considers the results using the secondary definition to be at less at risk of bias from informative censoring than the primary definition.

The ERG also notes the company's comments regarding PFS in the CS (p63) and in its response to the ERG clarification letter:

> "With regard to response, when assessing immunotherapies in clinical practice, this will be largely 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. Patients were permitted to receive treatment beyond RECIST-defined progression in CheckMate 214 as a reflection of this practice. However, it is important to note that progression assessments of immunotherapies against RECIST criteria for tumour progression in clinical trials therefore provide a conservative estimate of benefit from therapy compared to clinical practice assessment of immunotherapy treatment effect; this should be considered when interpreting PFS data."

> "… in this disease settings, [PFS] does not provide a great indicator of clinical benefit."

Clinical advice to the ERG is in broad agreement with both these comments from the company.

Investigator assessed PFS using the secondary definition (without censoring for subsequent therapy) is preferred by the ERG for modelling cost effectiveness. The rationale for this is presented in Section 5.5.3 of this ERG report.

4.6.3 Objective response rate in intermediate/poor risk patients

The IRRC-assessed ORR was 41.6% (95% CI: 36.9 to 46.5) in the NIVO+IPI arm and 26.5% (95% CI: 22.4 to 31.0) in the sunitinib arm (p<0.0001). A complete response was seen in 40 (9.4%) NIVO+IPI patients and in 5 (1.2%) sunitinib patients. A summary of best overall response is presented in Table 7.

Table 7 Best overall response in the CheckMate 214 trial, intermediate/poor risk patients

	NIVO+IPI (n=425)	Sunitinib (n=422)
Complete response	40 (9.4)	5 (1.2)
Partial response	137 (32.2)	107 (25.4)
Stable disease	133 (31.3)	188 (44.5)
Progressive disease	83 (19.5)	72 (17.1)
Unable to determine	31 (7.3)	50 (11.8)
Not reported	1 (0.2)	0
ORR, % (95% CI)	41.6 (36.9 to 46.5)	26.5 (22.4 to 31.0)
Difference of ORR, % (95% CI)	[redacted]	
p-value	<0.0001	

CI=confidence interval; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors
Source: CS, adapted from Table 9

Median TTR was 2.8 months and 3.0 months in the NIVO+IPI and sunitinib arms, respectively. Median DoR was not reached and 18.2 months in the NIVO+IPI and sunitinib arms, respectively.

At the time of analysis, 72% of responding patients in the NIVO+IPI arm had an ongoing response, in comparison to 63% of responding patients in the sunitinib arm. Therefore, 30.1% of patients in the NIVO+IPI arm and [redacted]% of patients in the sunitinib arm can be classified as "durable responders", defined as patients who initially responded to treatment and who were still responding at the time of the data cut-off (7 August 2017).

Investigator-assessed ORR was consistent with ORR as assessed by IRRC. Investigator-assessed ORR was [redacted]% (95% CI: [redacted]) in the NIVO+IPI arm and [redacted]% (95% CI: [redacted]) in the sunitinib arm.

4.6.4 Results for intermediate and poor risk patient subgroups from the CheckMate 214 trial

As part of the clarification process, the ERG requested that the company provide specific data from the CheckMate 214 trial for intermediate and poor risk groups separately, as discussed previously in Section 3.6 of this ERG report. The company provided these analyses but highlighted the following:

- the subgroups were not highlighted as of interest in the final scope issued by NICE
- the time and resources available to both the company and the ERG at the clarification process stage are not sufficient for appropriately rigorous consideration of fundamental scoping issues and their implications for decision making
- an analysis by subgroups appears to be redundant given the licensed population (and cost effectiveness results)
- the data presented for the OS HRs for both intermediate and poor risk groups separately "indicates no evidence of a difference between the groups and there is a clear *statistically and clinically meaningful* overall survival benefit in both groups, individually and combined"
- there is a "small difference" in the PFS HRs for the intermediate and poor risk subgroups
- in this disease setting, PFS does not provide a great indicator of clinical benefit (and PFS does not have a substantial impact on the cost-effectiveness results either)
- the results should be interpreted with caution as the analyses were post-hoc analyses.

In addition, the ERG notes that the PH assumption is violated for the intermediate risk group for OS and for both risk groups in both the IRRC-assessed primary definition of PFS and the investigator-assessed secondary definition of PFS (See Appendix 2, Sections 9.2.6 to 9.2.11).

A summary of OS and PFS results is provided in Table 8 for the intermediate risk and the poor risk subgroups separately. The ERG concurs with the company's interpretation of the OS results above. As in the analysis of the intermediate/poor risk patients, there was [redacted] (according to both the primary and secondary definitions, for assessments by investigator and by IRRC) between arms in intermediate risk patients. There was, however, [redacted] for NIVO+IPI versus sunitinib in terms of PFS (according to both the primary and secondary definitions, for assessments by investigator and by IRRC) for the poor risk patient subgroup.

The company also provided the number of patients treated beyond progression stratified by risk group (intermediate risk group: [redacted] of patients in the NIVO+IPI arm and [redacted] of patients in the sunitinib arm; poor risk group: [redacted] of patients in the NIVO+IPI arm and [redacted] of patients in the sunitinib arm). The ERG notes that the proportion of patients treated beyond progression was [redacted] in the intermediate risk group than in the poor risk group for both arms of the trial; however, this difference was [redacted] in the sunitinib arm.

Table 8 Summary of OS and PFS stratified by IMDC risk status

Outcome	Intermediate risk		Poor risk	
	NIVO+IPI (n=334)	Sunitinib (n=333)	NIVO+IPI (n=91)	Sunitinib (n=89)
OS				
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
IRRC-assessed PFS (primary definition)				
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
IRRC-assessed PFS (secondary definition)				
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
Investigator-assessed PFS (primary definition)				
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
Investigator-assessed PFS (secondary definition)				
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

CI=confidence interval; HR=hazard ratio; IMDC=International Metastatic RCC Database Consortium; IRRC=independent radiology review committee; NE=not evaluable; NR=not reached; NIVO+IPI=nivolumab+ipilimumab; OS=overall survival; PFS=progression-free survival; RCC=renal cell carcinoma
Source: Company response to the ERG clarification letter, questions A8-A12

The ERG observes that the types of subsequent therapy received by patients on disease progression were similar between intermediate and poor risk patient subgroups in the NIVO+IPI arm (Appendix 4, Section 9.4 of this ERG report). The ERG also considers that the types of subsequent therapy received by patients who were censored [redacted] between intermediate and poor risk patient subgroups (Appendix 4, Section 9.4 of this ERG report).

Results for IRRC-assessed ORR stratified by IMDC risk status are provided in Table 9. The results for best overall response for the intermediate and poor risk groups were broadly in line with those reported for the intermediate/poor risk group as a whole. However, it was notable that ORR for patients treated with sunitinib in the poor risk group was [redacted] than was reported for the intermediate (or intermediate/poor) risk group.

Table 9 Summary of best overall response stratified by IMDC risk status

Outcome	Intermediate risk		Poor risk	
	NIVO+IPI (n=334)	Sunitinib (n=333)	NIVO+IPI (n=91)	Sunitinib (n=89)
Complete response	[redacted]	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference of ORR, % (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

CI=confidence interval; NIVO+IPI=nivolumab + ipilimumab; ORR=objective response rate
Source: Company response to the ERG clarification letter, question A13

Overall, the ERG agrees that all of the results for intermediate and poor risk groups separately (including analyses taking into account subsequent therapy and ORR) should be interpreted with caution, as the analyses were post-hoc analyses (requested by the ERG). Therefore, the results from the intermediate/poor risk group combined are considered to be the most appropriate results to consider for decision making, particularly given NIVO+IPI is anticipated to be licensed for this population as a whole. The ERG therefore considers results from the intermediate/poor risk group are the most appropriate results for cost effectiveness analysis, particularly considering the immaturity of the OS data.

4.6.5 Results for patients with favourable risk status

As noted in Section 3.2, the anticipated licence for NIVO+IPI is only for patients with intermediate/poor risk status advanced RCC. However, as noted in Sections 4.3, the CheckMate 214 trial did also include 249 patients with favourable risk status and a pre-planned exploratory analysis of OS and PFS in this subgroup was also conducted. In summary, the results presented in the CS (Section B.2.7) showed that OS, PFS and ORR all favoured sunitinib. The difference in PFS was reported to be statistically significant (median PFS 15.3 months in NIVO+IPI arm and 25.1 months in sunitinib arm; HR=2.18, 99.1% CI: 1.29 to 3.68). The ERG notes that the statistical significance of this result should be interpreted with caution, as these exploratory analyses were not taken into consideration in the trial's alpha splitting strategy to control the overall Type 1 error rate in the study. While ORR favoured sunitinib (NIVO+IPI 28.8% and sunitinib 51.6%), [redacted]

4.6.6 Results for efficacy endpoints by PD-L1 tumour expression

Overall survival

In intermediate/poor risk patients, median OS for ≥1% PD-L1 tumour expression was [redacted] in the NIVO+IPI arm, and was [redacted] months in the sunitinib arm (HR=[redacted]). For patients with <1% PD-L1 tumour expression, median OS was [redacted] in either arm (HR=[redacted]). These results suggest that [redacted]. The company presents K-M curves for OS in patients with PD-LI ≥1% and in patients with PD-L1 <1% in Figure 10 and Figure 11 of the CS, respectively. The company states that these data support previous observations that PD-L1 is not a predictive biomarker for the treatment effect of nivolumab in advanced RCC. Clinical advice to the ERG is that advanced RCC patients would not be treated differently depending on PD-L1 status.

Progression-free survival

In intermediate/poor risk patients, the results of subgroup analyses suggest that the treatment effect of NIVO+IPI on IRRC-assessed PFS, in comparison to sunitinib, is more pronounced in patients with PD-L1 tumour expression ≥1%. For patients with PD-L1 tumour expression ≥1%, median PFS was 22.8 months in the NIVO+IPI arm, and 5.85 months in the sunitinib arm (p=0.0003). In patients with <1% PD-L1 tumour expression, median PFS was 11.0 months and 10.4 months in the NIVO+IPI and sunitinib arms, respectively. The company provides K-M curves for PFS by PD-L1 tumour expression in Appendix E of the CS.

Objective response rate

In intermediate/poor risk patients with PD-L1 tumour expression ≥1%, an objective response was seen in 58.0% of patients in the NIVO+IPI arm, in comparison to 21.9% of patients in the sunitinib arm (odds ratio [OR]=[redacted], 95% CI: [redacted]). In patients with PD-L1 tumour expression <1%,37.3% of NIVO+IPI patients had an objective response compared to 28.4% of sunitinib patients (OR: [redacted]; 95% CI: [redacted]).

4.6.7 Adverse events reported in the CheckMate 214 trial

Safety data for the CheckMate 214 trial are reported in the CS, Section B.2.10 and also in Appendix F to the CS.

Summary of adverse events

A summary overview of all AEs and deaths is presented in Table 14 of the CS and reproduced in Table 10 of this ERG report. The ERG notes that the reported proportions of patients with each type of AE presented [redacted] in the overall trial population as in the intermediate/poor risk group.

As shown in Table 10, the vast majority of patients in both treatment arms reported at least one any Grade AE. [redacted] patients reported any Grade 3 to 4 AEs, treatment-related AEs (TRAEs) or Grade 3 to 4 TRAEs in the NIVO+IPI arm than the sunitinib arm. However, [redacted] patients reported serious AEs (SAEs), Grade 3 to 4 SAEs, treatment-related SAEs (TRSAEs) and Grade 3 to 4 TRSAEs in the NIVO+IP arm than the sunitinib arm. There were [redacted] TRAEs leading to discontinuation of treatment in the NIVO+IPI arm than the sunitinib arm (data only presented for all risk patients for treatment discontinuations).

Table 10 Summary of adverse events in the CheckMate 214 trial

Type of adverse event, n (%)	Intermediate-/poor-risk patients		All treated patients	
	NIVO+IPI (n=423)	Sunitinib (n=416)	NIVO+IPI (n=547)	Sunitinib (n=535)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 to 4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Any TRAE	[redacted]	[redacted]	509 (93.1)	521 (97.4)
Grade 3 to 4 TRAE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 to 4 SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TRSAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 to 4 TRSAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	NR	NR	[redacted]	[redacted]
TRAE leading to discontinuation	NR	NR	[redacted]	[redacted]

AE=adverse event, SAE=serious adverse event; TRAE=treatment-related AE; TRSAE=treatment-related serious adverse event
Source: CS, adapted from Table 14

Common types of treatment-related adverse events

The frequency of TRAEs occurring in ≥15% of the CheckMate 214 trial participants reported in the CS are described in Table 15 of the CS. The ERG notes that the reported proportions of patients with each type of AE presented [redacted] in the overall trial population and in the intermediate/poor risk group.

In the intermediate/poor risk population, the most frequently reported TRAEs in the NIVO+IPI arm were [redacted]. In the sunitinib arm, the most frequently reported TRAEs were [redacted]. The most common Grade 3 to 4 TRAEs (occurring in ≥1.5% of intermediate/poor risk patients) were [redacted] in the NIVO+IPI arm. In the sunitinib arm, [redacted] were the most commonly reported Grade 3 to 4 TRAEs.

Immune-mediated adverse events

Given the mechanism of action of NIVO+IPI, a summary of select IMAEs is presented in Table 16 of the CS and reproduced in Table 11 of this ERG report. The ERG notes that the company only presents details of the IMAEs experienced by all patients. Three types of IMAE occurred in ≥15% patients: hypothyroidism (19%) and rash (17%) with NIVO+IPI and [redacted] with sunitinib. The majority of IMAEs were reported to be Grade 1 to 2 in severity, with hepatitis and diarrhoea/colitis being the only two Grade 3 to 4 IMAEs to be reported by ≥5% of patients in the NIVO+IPI arm (6% and 5%, respectively). All types of Grade 3 to 4 IMAEs occurred in <1% of patients in the sunitinib arm.

The ERG observes that the frequency of IMAEs differs slightly to the incidence of TRAEs in some instances. During the clarification process, the company explained that the IMAEs were defined as specific events regardless of causality, occurring within 100 days of the last dose, that may involve any organ system including skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories. The company further clarified that TRAEs were defined as an AE with a reasonable causal relationship to study drug administration, as determined by a physician, and therefore not all TRAEs would be defined as IMAEs.

Table 11 Immune-mediated adverse events in the CheckMate 214 trial

Type of immune-mediated adverse event, n (%)	All treated patients			
	NIVO+IPI (n=547)		Sunitinib (n=535)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Rash	93 (17)	16 (3)	[redacted]	[redacted]
Diarrhoea/colitis	55 (10)	27 (5)	[redacted]	[redacted]
Hepatitis	38 (7)	33 (6)	[redacted]	[redacted]
Nephritis and renal dysfunction	27 (5)	11 (2)	[redacted]	[redacted]
Pneumonitis	22 (4)	11 (2)	[redacted]	[redacted]
Hypersensitivity/infusion reaction	5 (1)	0 (0)	[redacted]	[redacted]
Hypothyroidism	104 (19)	3 (0.5)	[redacted]	[redacted]
Hyperthyroidism	66 (12)	4 (0.7)	[redacted]	[redacted]
Adrenal insufficiency	44 (8)	16 (3)	[redacted]	[redacted]
Hypophysitis	27 (5)	16 (3)	[redacted]	[redacted]
Thyroiditis	16 (3)	1 (0.2)	[redacted]	[redacted]
Diabetes mellitus	16 (3)	5 (1)	[redacted]	[redacted]

Source: CS, Table 16

Treatment-related deaths

As reported in Appendix F to the CS, in the intermediate/poor risk population, there were [redacted] ([redacted]) treatment-related deaths in the NIVO+IPI arm and [redacted] ([redacted]) treatment-related deaths in the sunitinib arm. Consistent with the all risk population, disease progression was the most common cause of death for both groups.

The ERG notes that the reasons for death in the all risk population are provided in the published paper by Motzer et al (2018). There were eight treatment-related deaths in the NIVO+IPI arm and four treatment-related deaths in the sunitinib arm. Reasons given for death in seven patients in the NIVO+IPI arm were pneumonitis, immune-mediated bronchitis, lower gastrointestinal hemorrhage, hemophagocytic syndrome, sudden death, liver toxic effects and lung infection. The cause of death for the eighth patient was pneumonia and aplastic anemia, which was updated after the database lock to treatment-related, therefore only seven treatment-related deaths were reported in the CS. In the sunitinib arm, two reasons for death were attributed to cardiac arrest, one reason for death was attributed to heart failure and another reason for death attributed to multiple organ failure.

Safety overview

Overall, the company considers that the overall safety of NIVO+IPI is acceptable compared to sunitinib, and reports no new safety concerns. The company considers that the majority of the IMAEs were [redacted].

The company argues that [redacted] treatment-related discontinuations due to an AE in the NIVO+IPI arm than in the sunitinib arm, the mean number of ipilimumab doses received by the overall trial population was 3.6 (of a total of 4), indicating that the treatment was generally well-tolerated. It is also noted by the company and supported by clinical advice that although some additive toxicity can be expected, the safety profile of the combination of NIVO+IPI reported in the CheckMate 214 trial was generally consistent with that observed with its use in other indications.

The ERG notes that the proportions of all AEs including the most common types of TRAEs did not greatly differ when comparing incidences in the intermediate/poor risk and overall trial populations. However, it was not possible to determine if this was also the case for IMAEs where data are only reported for the overall trial population. The ERG also notes that in the published paper it is reported that 35% of patients in the NIVO+IPI arm who had a treatment-related IMAE required high-dose corticosteroids to manage side effects (≥40 mg of prednisone per day or equivalent). High-dose corticosteroids may themselves negatively impact HRQoL as they are also associated with side effects.

Clinical opinion to the ERG advised that the toxicity profiles of NIVO+IPI and sunitinib are very different and therefore make direct comparison challenging. However, broadly, the combination of NIVO+IPI appears to be less toxic than sunitinib. Many AEs associated with

sunitinib are largely predictable and correlate with increasing exposure. They tend to occur early during treatment and be persistent whilst patient is on therapy, which can adversely affect their HRQoL. However, AEs with immune checkpoint inhibitors are largely controllable and correlate less well with exposure and tend to be idiosyncratic and unpredictable. They do not tend to be chronic in nature but occur sporadically and unexpectedly. They are characteristically transient but occasionally can be moderate or severe (e.g. endocrinopathies, diarrhoea, colitis, hepatitis, pneumonitis, interstitial nephritis, and rash). It is also noted that even after stopping treatment, patients may still experience benefit (and therefore harm) from treatment with immune checkpoint inhibitors because they have previously responded to treatment (immunological memory).[103,104]

4.6.8 Health-related quality of life

HRQoL data derived from the FKSI-19 are reported for the intermediate/poor risk group and EQ-5D-3L and FACT-G data are reported for the overall trial population.

Functional Assessment of Cancer Therapy – Kidney Symptom Index findings (intermediate/poor risk group)

The rate of completion of the FKSI-19 questionnaire, which assesses symptoms of importance to patients with advanced kidney cancer, exceeded 80% in both treatment arms during the first 6 months. In the CS it is reported that, from Week 8 onwards, NIVO+IPI provided a [redacted] in disease symptoms over time whereas in the sunitinib arm, average scores indicated [redacted]. Motzer et al (2018) report that in the intermediate/poor risk group, the mean change from baseline was greater in the NIVO+IPI arm than in the sunitinib arm at each assessment during the first 6 months ($p<0.001$).

EQ-5D-3L findings (all risk group)

[redacted]

Functional Assessment of Cancer Therapy-General questionnaire findings (all risk group)

The FACT-G questionnaire was reported to be completed by [redacted] of patients in the NIVO+IPI arm and [redacted] of patients in the sunitinib arm. Over the first year of follow-up, approximately [redacted] of the HRQoL assessments during NIVO+IPI treatment exceeded baseline values, and [redacted] of the assessments during sunitinib treatment exceeded baseline values, indicating [redacted] for patients treated with NIVO+IPI.

HRQoL overview

Using all of the HRQoL data collected, the results show that HRQoL was [redacted] over time for patients treated with NIVO+IPI compared with patients treated with sunitinib. However, the ERG cautions that only patients who remained on treatment were asked to complete the questionnaires (although they were asked to completed questionnaires on two occasions after their last dose). Thus, while response rates to the HRQoL instruments are high, the number of eligible patients (that constitute the denominator to calculate response rates) reduced markedly over time. For example, the proportion of patients “at risk”, i.e. eligible to complete the FKSI-19 questionnaire, was 54% after 24 weeks (approximately 6 months), 35% after 48 weeks (approximately 1 year) and 8% after 104 weeks (2 years). Therefore, the HRQoL results must be treated with a degree of caution, particularly results from 24 weeks and beyond.

4.7 ERG critique of the indirect evidence

4.7.1 The company's original NMAs

Due to a lack of clinical trials comparing NIVO+IPI with pazopanib directly, the company performed NMAs to obtain relative estimates of effect for this comparison.

In addition to the CheckMate 214 trial, 45 trials were included in the final evidence base identified via the company's systematic literature review. The company's NMAs included data from 37 trials; the remaining nine trials were excluded from the analyses due to reporting neither a HR nor a K-M curve for PFS or OS.

The company's base-case NMAs for the outcomes of PFS and OS included only RCTs that provided survival data for intermediate/poor risk advanced RCC patients. The company also performed two sensitivity analyses and secondary analyses for each outcome; each of these analyses included RCTs that reported data for all randomised patients, regardless of risk group, hereafter referred to as the "all risk" patient group. A summary of the methodology for each of these analyses, and the number of trials included in each analysis is provided in Table 12.

Table 12 Summary of the company's conducted NMAs

	Methodology	Number of trials included in the NMA[a]	
		OS	PFS
Base-case	Only trials reporting data for the intermediate/poor risk group are included in this NMA	6 trials	13 trials
Sensitivity analysis 1	• Only trials that report data for either the intermediate/poor risk group, or for the all risk group, that reported the proportion of favourable risk patients, are included in this NMA • Meta-regression was performed to account for the proportion of patients with favourable MSKCC prognostic factors in the trials that do not report data for intermediate/poor risk patients	15 trials	25 trials
Sensitivity analysis 2	• Only trials reporting data for the all risk group, that reported the proportion of favourable risk patients, are included in this NMA • Meta-regression was performed to account for the proportion of patients with favourable MSKCC prognostic factors in each included trial	15 trials	25 trials
Secondary analysis	All trials reporting data for the all risk group are included in this NMA	28 trials	25 trials

MSKCC=Memorial Sloan Kettering Cancer Center; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival

[a] The number of trials included in each NMA was obtained from the data input tables included in Appendix D of the CS (Tables 5-8)

When considering the network diagrams for the two sensitivity analyses and the secondary analyses for each outcome (provided in Appendix D of the CS, Figures 2 to 7), the number of trials in the network diagram often differs to the number of trials included in the data input table. The ERG notes that the network diagrams for the base-case analyses match the data

input table for both OS and PFS, and so is confident that six trials were included in the base-case analysis for OS, and 13 trials were included in the base-case analysis for PFS.

The ERG notes that, of these analyses, only the base-case analyses were designed to derive HRs applicable to the relevant patient population (patients with intermediate/poor risk advanced RCC). However, for the OS base-case analysis, the company explains that it was not possible to estimate a HR for NIVO+IPI versus pazopanib due to a lack of data. For the PFS base-case analysis, the ERG requested clarification from the company about the data inputted from the COMPARZ trial, which compares pazopanib with sunitinib. The company explained that the HR from COMPARZ that was used in the PFS base-case analysis was applicable to intermediate risk patients only. Therefore, the PFS base-case analysis includes no data for poor risk patients from the COMPARZ trial, which led the ERG to question the applicability of the HR for NIVO+IPI versus pazopanib obtained from this analysis to the relevant patient population. Therefore, none of the company's originally conducted NMAs are able to derive a HR for NIVO+IPI versus pazopanib in the relevant patient population.

4.7.2 ERG requested indirect comparisons

Since the CheckMate 214 trial compares NIVO+IPI to sunitinib, and the COMPARZ trial compares sunitinib to pazopanib, the ERG observed that it would be possible to link NIVO+IPI and pazopanib in a simple network including only the CheckMate 214 and COMPARZ trials. According to guidance in NICE Technical Support document 1,[105] there is no specific need to include comparators other than those relevant to the decision problem in the network, unless such an extension is required to produce a connected network. The disadvantage of extending the network to include comparators other than those relevant to the decision problem is the possibility that effect modifiers will be introduced; trials of more remotely connected treatments are likely to have different patient populations compared to the patient population of interest.

However, the ERG also noted that OS and PFS HRs have not been published for the subgroup of intermediate/poor risk patients from the COMPARZ trial. In the company's base-case analyses, the company used a HR for PFS for intermediate risk patients only, derived from Figure S3 of the supplementary appendix of the COMPARZ trial using graph digitising software. The company used this HR for intermediate risk patients only as a proxy for a HR for intermediate/poor risk patients in the base-case PFS analysis. The company did not obtain a HR for intermediate/poor risk patients for OS. The ERG is disappointed that the company did not contact the COMPARZ trial authors to attempt to obtain an HR for intermediate/poor risk patients for either OS or PFS.

The ERG identified that in a letter by Motzer et al (2014),[106] OS HRs from the COMPARZ trial were available for intermediate risk patients, and poor risk patients separately. Therefore, it is possible to perform meta-analysis of these HRs and obtain a HR for the intermediate/poor risk population. As part of the ERG's clarification letter to the company, the ERG requested that the company perform indirect comparisons for OS using data from the letter by Motzer et al[106] and the CheckMate 214 trial data in the following patient populations:

1. Poor risk patient population.
2. Intermediate risk patient population.
3. Intermediate/poor risk patient population

For IRRC-assessed PFS, the ERG requested that the company perform two indirect comparisons using:

1. the HR for the intermediate risk patient population from the supplementary appendix of the COMPARZ trial,[5] and the CheckMate 214 trial data for the intermediate risk patient population.
2. the HR for the intermediate risk patient population from the supplementary appendix of the COMPARZ trial,[5] and the CheckMate 214 trial data for the intermediate/poor risk patient population.

The ERG requested that the company conduct each of the above indirect comparisons using both the primary and secondary definitions of PFS for the CheckMate 214 trial. The company provided these analyses in their response to the ERG clarification letter.

Due to the additional heterogeneity that would be introduced by including comparators other than those relevant to the decision problem in the network, the ERG considers the ERG requested indirect comparisons to be more appropriate for generating estimates of treatment effectiveness for NIVO+IPI in comparison to pazopanib than the company's originally submitted NMAs. Furthermore, the ERG identified that the company had incorrectly extracted a HR that was incorporated in the company's originally submitted PFS NMAs, and as discussed above, the number of trials included in each network diagram often differs to the number of trials included in the data input table. For these reasons, the ERG does not present the results of the company's originally submitted NMAs in this report.

The ERG's requested indirect comparisons are discussed further in Sections 4.7.3 to 4.7.7 of this ERG report.

4.7.3 Studies included in the ERG requested indirect comparisons

The studies included in the ERG requested indirect comparisons were the CheckMate 214 trial, and the COMPARZ trial. Trial characteristics of the CheckMate 214 trial are provided in Section 4.3.1 of this ERG report.

The COMPARZ trial was an international, multicentre, Phase III, open-label non-inferiority trial investigating the comparative efficacy and safety of pazopanib versus sunitinib.[5] The study enrolled treatment-naïve adult patients (≥18 years) with clear-cell advanced/metastatic RCC and good performance status (KPS score ≥70). Patients were randomised in a 1:1 ratio to pazopanib (n=557) or sunitinib (n=553). The primary outcome of the COMPARZ trial was PFS assessed by IRRC, and key secondary outcomes included ORR and OS.

4.7.4 Methodological approach to the ERG requested indirect comparisons

The company conducted the ERG requested indirect comparisons using the Bucher adjusted indirect comparison method,[107] in which the indirect comparison of treatments A and C is adjusted according to the results of their direct comparisons with a common comparator treatment, B. The log HR of treatments A and C is calculated using the following formula:

$$\ln\left(HR_{A,C}\right) = \ln\left(HR_{A,B}\right) - \ln\left(HR_{C,B}\right)$$

The standard error of the log HR is given by:

$$SE(ln\left(HR_{A,C}\right)) = \sqrt{SE(ln\left(HR_{A,B}\right))^2 + SE(ln(HR_{C,B}))^2}$$

For the meta-analysis of the two OS HRs reported in the letter by Motzer ,et al (2014)[106] the company used the inverted variance weighting method to obtain the HR for pazopanib versus sunitinib in the intermediate/poor risk patient population. The method can be summarised as follows:

$$\ln(HR_{pooled}) = \frac{\sum wt_i \ln(HR_i)}{\sum wt_i}$$

with the weight of $\ln(HR_i)$ defined as $wt_i = 1/SE(\ln(HR_i))$.

The standard error of the log HR given by:

$$SE(\ln(HR_{pooled})) = \frac{1}{\sum wt_i}$$

The ERG considers the company's approach to the ERG requested indirect comparisons to be appropriate.

4.7.5 Characteristics of patients enrolled in the studies included in the ERG requested indirect comparisons

The characteristics of intermediate/poor risk patients enrolled in the CheckMate 214 trial were previously described in Section 4.3 where it was noted that, in terms of baseline data collected, patient characteristics were broadly similar to those of the overall trial population. Baseline characteristics in the COMPARZ trial were only reported for patients of all risk status. With the possible exception that approximately 83% of patients had prior nephrectomy in the COMPARZ trial, compared with approximately 92% in the CheckMate 214 trial (all risk populations), the patient characteristics of all risk patients recorded in both trials were similar. This includes the proportions of patients classified as being at intermediate risk (61% in both trials when those without a risk classification are excluded) although the COMPARZ trial appeared to have proportionately fewer poor risk patients (16% in the CheckMate 214 trial and 11% in the COMPARZ trial when those without a risk classification are excluded). It should be noted that risk status was assigned using the IMDC model in the CheckMate 214 trial and using the MSKCC model in the COMPARZ trial. A comparison of patient characteristics is presented in Appendix 3 (Section 9.3), Table 41 of this ERG report.

4.7.6 Assessment of risk of bias of the trials included in the ERG requested indirect comparisons

As previously noted (Section 4.4), the company assessed the risk of bias of the CheckMate 214 trial using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[94] The company used the same criteria to assess the risk of bias of the COMPARZ trial (Table 13). As with the CheckMate 214 trial, overall, the ERG considers that the COMPARZ trial was generally well designed and well conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for most domains. However, the open-label design provides the opportunity for subjective results and investigator-assessed outcomes to be biased. The ERG requested indirect comparisons were conducted for IRRC-assessed PFS, and OS. IRRC assessments were conducted in a blinded manner, and OS is an objective outcome, so the lack of blinding in the COMPARZ trial is not a concern for the ERG requested indirect comparisons.

Table 13 Assessment of risk of bias for the COMPARZ trial

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Not available	Agree, there is insufficient information provided in the trial report so risk of bias is unclear for this domain
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree, the open-label nature of the trials provides an opportunity for subjective results and investigator-assessed outcomes to be biased
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree, the full study protocol outlining pre-specified outcomes is provided in the supplementary materials to the COMPARZ trial publication
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Agree
Were appropriate methods used to account for missing data (LOCF, MMRM)?	Yes	Agree

Source: CS, Appendix D (Table 15) and ERG comment

4.7.7 Results from the ERG requested indirect comparisons

The data inputs and results of the ERG requested indirect comparisons for OS are provided in Table 14.

Table 14 Inputs and results of the ERG requested indirect comparisons for OS

Patient population	NIVO+IPI versus sunitinib		Pazopanib versus sunitinib		HR from the indirect comparison for NIVO+IPI versus pazopanib (95% CI)
	HR (95% CI)	Source	HR (95% CI)	Source	
Poor risk	[redacted]	CheckMate 214 trial data	0.85 (0.56 to 1.28)	Motzer et al (2014) letter [106]	[redacted]
Intermediate risk	[redacted]	CheckMate 214 trial data	0.90 (0.74 to 1.09)	Motzer et al (2014) letter [106]	[redacted]
Intermediate/ poor risk	[redacted]	CheckMate 214 trial data	0.89 (0.75 to 1.06)	Meta-analysis conducted by the company (clarification response, question A17) of intermediate and poor risk HRs presented in Motzer et al (2014) letter[106]	[redacted]

Source: Company response to the ERG clarification letter, question A17
CI=confidence interval; HR=hazard ratio; OS=overall survival

The results of the indirect comparison suggest that NIVO+IPI significantly improves OS in the intermediate/poor risk patient population in comparison to pazopanib. There were no

significant differences in the intermediate risk or poor risk patient populations considered separately. However, the ERG notes that neither trial was powered to detect differences in either the intermediate or poor risk patient subgroups when considered separately.

The data inputs and results of the ERG requested indirect comparisons for IRRC-assessed PFS are provided in Table 15.

Table 15 Inputs and results of the ERG requested indirect comparisons for IRRC-assessed PFS

Patient population	NIVO+IPI versus sunitinib		Pazopanib versus sunitinib		NIVO+IPI versus pazopanib
	HR (95% CI)	Source	HR (95% CI)	Source	HR from the indirect comparison (95% CI)
PFS (primary definition)					
Intermediate risk	[redacted]	CheckMate 214 trial data	0.98 (0.80 to 1.19)	Supplementary appendix (Figure S3) of COMPARZ	[redacted]
Intermediate risk from COMPARZ and intermediate/poor from CheckMate	[redacted]	CheckMate 214 trial data	0.98 (0.80 to 1.19)	Supplementary appendix (Figure S3) of COMPARZ	[redacted]
PFS (secondary definition)					
Intermediate risk	[redacted]	CheckMate 214 trial data	0.98 (0.80 to 1.19)	Supplementary appendix (Figure S3) of COMPARZ	[redacted]
Intermediate risk from COMPARZ and intermediate/poor from CheckMate	[redacted]	CheckMate 214 trial data	0.98 (0.80 to 1.19)	Supplementary appendix (Figure S3) of COMPARZ	[redacted]

Source: Company response to the ERG clarification letter, question A17
CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

The results of the indirect comparisons show no significant differences between NIVO+IPI and pazopanib for any of the analyses conducted for IRRC-assessed PFS. However, the ERG notes that neither trial was powered to detect differences in the intermediate risk patient subgroup.

The company highlighted further limitations of the ERG requested indirect comparisons in their response to the ERG clarification letter. Firstly, patient characteristics were not reported for the intermediate and poor risk groups of the COMPARZ trial separately, or indeed for the intermediate/poor risk patient subgroup. Thus, it was not possible to compare patient demographics between the COMPARZ and CheckMate 214 trials for any of the OS and PFS indirect comparisons. Therefore, potential bias due to unbalancing of treatment confounders between the two populations might exist which could bias the results of all the indirect

comparisons. The ERG agrees with the company that this issue is a limitation of the ERG requested indirect comparison. However, the ERG notes that the characteristics of patients included in the following populations: the CheckMate 214 trial intermediate/poor risk group, the CheckMate 214 trial all risk group, and the COMPARZ trial all risk group, were broadly comparable. Therefore, there is no evidence to suggest that there are important differences between the populations compared in each indirect comparison from the two trials.

The company also highlighted that two of the indirect comparisons for PFS used a HR for NIVO+IPI versus sunitinib in the intermediate/poor risk patients while the HR for pazopanib versus sunitinib came from the intermediate risk patient group. Once again, the ERG agrees with the company that this is an important limitation; however, the ERG considers that the ERG requested indirect comparisons are the best ways to obtain estimates of relative effectiveness for NIVO+IPI versus pazopanib in the relevant patient population considering the available data. The ERG notes that if the company had contacted the COMPARZ trial authors to attempt to obtain an HR for intermediate/poor risk patients for either OS or PFS, then it might have been possible to conduct indirect comparisons across consistent patient populations.

Finally, the company highlights that the definition of PFS in the COMPARZ and CheckMate 214 trials might be different. The ERG notes that PFS in the COMPARZ trial is “the period between the date of randomisation and the date of the first documentation of disease progression or death from any cause”, which is identical to the definition used in the CheckMate 214 trial. Further, all HRs used as data inputs in the indirect comparisons were for PFS as assessed by IRRC. However, information on censoring is not available in the published paper for the COMPARZ trial, so the ERG agrees with the company that the exact definitions of PFS may differ between the trials, and that this is also a limitation of the ERG requested indirect comparisons for PFS.

In conclusion, the ERG agrees that there are limitations to the ERG requested indirect comparisons. However, the ERG considers that the ERG requested indirect comparisons are more appropriate for obtaining estimates of relative effectiveness for NIVO+IPI versus pazopanib than the company’s original NMAs due to reasons outlined in Section 4.7.2 of this ERG report.

4.8 Conclusions of the clinical effectiveness section

Evidence for NIVO+IPI versus an appropriate comparator (sunitinib) has been presented from the CheckMate 214 trial for patients with intermediate/poor risk advanced RCC. No direct evidence is available comparing NIVO+IPI versus the other comparator of interest (pazopanib); indirect evidence has therefore been presented for this comparison.

Direct evidence has shown that, for patients with intermediate/poor risk advanced RCC, NIVO+IPI results in statistically significantly improved OS when compared with sunitinib (median OS not reached in the NIVO+IPI arm). However, given the immaturity of the OS data, it is unknown whether the OS benefit observed at the first-interim analysis of OS will be observed in the longer-term. The ERG notes that subsequent therapy received following disease progression may impact on OS. There is uncertainty to what extent the treatments received in the CheckMate 214 trial impacted upon OS. Furthermore, subsequent treatment received in both arms of the trial differed to what clinicians would expect patients to receive in clinical practice. There is therefore also uncertainty as to how similar OS reported in the trial would be to OS observed in clinical practice.

Median PFS differs noticeably in the NIVO+IPI arm when using IRRC-assessed data and investigator assessed data. Using the company's preferred primary definition of PFS (censoring data for subsequent therapy) or the secondary definition of PFS preferred by the ERG (no censoring of data for subsequent therapy), IRRC-assessed median PFS is ≥11 months. Using investigator-assessed PFS (primary definition), the median in the NIVO+IPI arm is approximately 8 months, similar to that of sunitinib; median PFS for the secondary definition by investigator assessment is not presented in the CS. IRRC and investigator assessed response data show a statistically significantly improved ORR for NIVO+IPI (41.6% and [redacted] respectively) versus sunitinib (26.5% and [redacted] respectively). Furthermore, there are a higher proportion of complete responders in the NIVO+IPI arm (9.4%) than in the sunitinib arm (1.2%) and 30.1% of patients in the NIVO+IPI arm can be classified as "durable responders" compared with [redacted]% of patients in the sunitinib arm.

Pre-specified subgroup analyses of the CheckMate 214 trial show that sunitinib may be more efficacious than NIVO+IPI for patients in the favourable risk group. This patient population is outside the scope of the current appraisal. Subgroup analyses by PD-L1 status show that both patients in the intermediate/poor risk group with PD-L1 tumour expression ≥1% or <1% have greater benefit with NIVO+IPI than with sunitinib, suggesting that PD-L1 status is not a useful biomarker for identifying patients who may most benefit.

Compared to the sunitinib arm, in the NIVO+IPI arm, [redacted] patients experienced TRAEs including Grade 3 to 4 TRAEs. [redacted] patients experienced TRSAEs including Grade 3 to 4 TRSAEs, IMAEs and treatment discontinuations. However, clinical advice to the ERG is that AEs with NIVO+IPI tend to occur sporadically and unexpectedly and are characteristically transient whereas AEs with sunitinib tend to be chronic. Therefore, the safety evidence from the CheckMate 214 trial suggests that NIVO+IPI appears to have acceptable tolerability when compared with sunitinib. Indeed, in the CheckMate 214 trial, HRQoL results show that HRQoL was [redacted] over time for patients treated with NIVO+IPI compared with patients treated with sunitinib.

To compare NIVO+IPI with pazopanib in the intermediate/poor risk group, an estimate of relative efficacy was derived from an indirect comparison using data from the CheckMate 214 and COMPARZ trials. Based on the baseline characteristics presented, patients in both trials appeared to be broadly similar, albeit baseline characteristic data were only available for patients in the all risk population in the COMPARZ trial. Similar to the findings from the direct evidence, the findings from the indirect comparison show NIVO+IPI to result in a statistically significant improvement in OS but not in PFS in comparison to pazopanib. However, PFS for pazopanib versus sunitinib in the COMPARZ trial (and therefore for the indirect comparison of NIVO+IPI with pazopanib) was only available for the intermediate risk group (not the intermediate/poor risk group). Furthermore, the exact definitions of PFS may have differed between trials. Indirect comparisons of NIVO+IPI versus pazopanib for ORR, AEs or HRQoL were not presented in the CS. Clinical advice to the ERG is that pazopanib is generally considered to be a more tolerable treatment than sunitinib (e.g. data derived from the COMPARZ trial and PISCES study).

The direct and indirect evidence appears to be generalisable to patients who would be treated in NHS practice with the following important caveats: patients in the trials tended to be younger than seen in clinical practice, had clear-cell disease and the proportion of patients who had prior nephrectomy may be greater than is now seen in clinical practice. The extent of the benefit for NIVO+IPI versus VEGFR-TKIs for older patients, patients with non-clear cell RCC and patients who have not had prior nephrectomy is therefore unknown.

A final uncertainty relates to the wording of the marketing indications for all currently available second-line treatment options for advanced RCC. All indications specify that patients must have been previously treated with VEGFR-TKI (such as sunitinib or pazopanib) or cytokine agent (such as high-dose interleukin-2). Therefore, if NIVO+IPI were recommended and the marketing indications of the currently recommended drugs were strictly adhered to (i.e. not

used off-label), then no treatment would be available to patients who did not respond to treatment with NIVO+IPI.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of NIVO+IPI for previously untreated patients with intermediate/poor risk advanced RCC. Two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Objective of the company's systematic review

The company performed a systematic review of the literature to identify studies that evaluated the cost effectiveness of treatment with NIVO+IPI for previously untreated patients with advanced RCC. The company initially searched the databases in Table 16 on 27 March 2017 and updated the searches on 5 October 2017.

Table 16 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Embase.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Embase.com
MEDLINE® In-Process	Pubmed.com
Cochrane Library	Wiley.com
National Health Service Economic Evaluation Database (NHS EED)	NHS EED
EconLit®	Ebsco.com

Source: CS, Appendix G

Only relevant studies published in English were included in the review. The publication period of interest was restricted to 2006 onwards.

The company also carried out searches to identify conference proceedings from 2015 to 2017 from:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Congress
- European Society for Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO).

Additionally, NICE, the Scottish Medicines Consortium (SMC) and the All Wales Medicine Strategy Group (AWMSG) websites were searched for potentially relevant HTA economic models. Details of the search strategies used by the company are provided in Appendix G of the CS.

5.1.1 Eligibility criteria used in study selection

The main inclusion criteria used to select studies are shown in Table 17. The ERG is satisfied that the criteria meet the objectives set out in the decision problem.

Table 17 Economic review inclusion and exclusion criteria

Characteristic	Inclusion criteria	Exclusion criteria
Population	• Adults with advanced RCC • Previously untreated	• Healthy volunteers • Paediatric population • Disease other than advanced RCC • Pre-treated patients
Interventions	• The list of included interventions was comprised of the following, whether alone or in combination with any other therapy: - ipilimumab - nivolumab - combination of ipilimumab and nivolumab	• Non-drug treatments (e.g. surgery, radiotherapy) • Studies assessing interventions not in the list
Comparator	• No restriction; all therapies were included	• No exclusions based on comparator
Outcomes	• Incremental costs, LYs gained and QALYs, and any other measure of effectiveness reporting together with costs • Model inputs • Sensitivity analysis	• Cost-only outcomes
Study design	• Full-economic evaluations (cost consequence, cost-effectiveness, cost utility, cost benefit) • Trial based economic evaluations	• Reviews, letters, and comment articles • Partial economic evaluations such as only cost analysis • Not an economic model
Country	• UK and Ireland	• Non-UK studies

LY=life years; QALY=quality adjusted life year
Source: CS Appendix G, Table 18

5.1.2 Included and excluded studies

The company did not identify any cost effectiveness studies that matched the final scope issued by NICE. Details of the screening process and the reasons for the exclusion of the studies are presented in Section B.3.1 and Appendix G of the CS.

However, the company identified four relevant appraisals of sunitinib (TA169), pazopanib (TA215), nivolumab (TA417) and tivozanib (ID591). The methods and data from these appraisals were used to inform the development of the company economic model. TA169 evaluates sunitinib versus bevacizumab, sorafenib or temsirolimus as first-line options for advanced RCC. TA215 compares pazopanib versus sunitinib, IFN-α or best supportive care as first-line treatments for advanced RCC. TA417 evaluates the use of nivolumab for previously treated advanced RCC and is the only previous STA that has appraised an immune checkpoint inhibitor for the treatment of RCC. ID591 was an ongoing appraisal of tivozanib

versus sunitinib and pazopanib as first-line treatments for RCC at the time of the CS but has since been completed as noted in Section 2.3 of this ERG report. Cohort-level portioned economic models were used in aforementioned appraisals.

5.1.3 Findings from the company's cost effectiveness review

The company did not identify any studies that evaluated the cost effectiveness of first-line treatment with NIVO+IPI for advanced RCC compared to any of the comparators. Summary details relating to the NICE technology appraisals considered to be relevant to the company's modelling approach (TA169, TA215, TA417 and ID591) are reported in the CS (Table 20).

5.1.4 ERG critique of the company's review of cost effectiveness evidence

The ERG considers that the databases searched and the search terms used appear to be reasonable. The ERG updated the searches and is satisfied that the company has not missed any relevant economic studies.

5.2 Summary and critique of the company's submitted economic evaluation

5.2.1 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with NIVO+IPI versus treatment with sunitinib or pazopanib in adults with previously untreated, intermediate/poor risk advanced RCC.

5.2.2 NICE reference case checklist

Table 18 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE: people with untreated, intermediate/poor risk (as per IMDC) advanced RCC	Yes
Comparator(s)	As listed in the scope developed by NICE: sunitinib or pazopanib	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Data primarily taken from CheckMate 214	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the company model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
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

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; IMDC=International Metastatic RCC Database Consortium; NMA=network meta-analysis; PSS=Personal social services; QALY=quality adjusted life year; RCC=renal cell carcinoma

5.2.3 Model structure

The company developed a cohort-based partitioned survival model in Microsoft Excel. The model assesses the incremental cost effectiveness of treatment with NIVO+IPI versus

treatment with sunitinib or pazopanib for previously untreated, intermediate/poor risk advanced RCC.

The model structure comprises six mutually exclusive health states designed to capture disease progression and treatment status, terminal care and death as shown in Figure 1. The modelled population enters the model progression-free and on first-line treatment (PFS On 1L Tx). At the end of every 1-week cycle, there is a risk of discontinuing first-line treatment due to unacceptable toxicity (transition to PFS Off 1L Tx) or disease progression (transition to PPS Off 1L Tx). Additionally, all modelled individuals on the NIVO+IPI arm who remain progression-free and on first-line treatment after 5 years also transit to the 'PFS Off 1L Tx' health state. The model allows disease progression to occur with and without the risk of discontinuing first-line treatment. For instance, patients could experience disease progression and remain on first-line therapy. A proportion of the cohort who are off first-line treatment (PFS or PPS) are assumed to receive second-line treatments. Terminal care is a temporary health state that captures additional cost associated with 8 weeks before all-cause mortality, from any of the PFS or PPS health states.

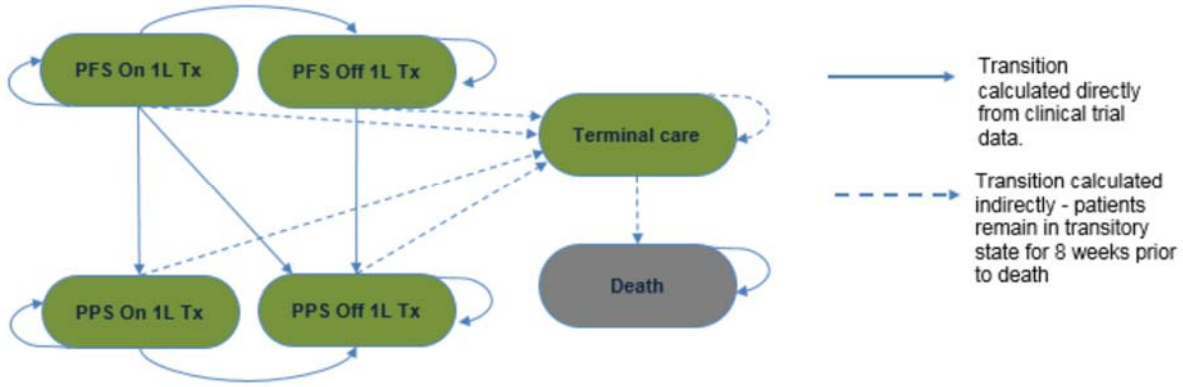

Figure 1 Health state structure of the company model

Source: CS, Figure 14

5.2.4 Population

Previously untreated patients with intermediate/poor risk advanced RCC are considered in the company model. The focus on patients with intermediate/poor risk advanced RCC is in line with the final scope issued by NICE. The mean baseline age of the cohort (60.5 years), the percentage of males (72.6%) and other baseline characteristics are based on the population recruited to the CheckMate 214 trial.

5.2.5 Interventions and comparators

Intervention

NIVO+IPI is implemented in the model as per the anticipated EMA marketing authorisation. Nivolumab (3mg/kg IV infusion) plus ipilimumab (1mg/kg IV infusion) is administered every 3 weeks for four cycles. Thereafter, nivolumab (3mg/kg IV infusion) is administered every 2 weeks.

Comparators

Sunitinib and pazopanib treatments are administered orally. People receiving sunitinib take 50mg once daily for the first 4 weeks of every 6-week treatment cycle while people receiving pazopanib take 800mg of their medication once daily (see CS, Sections B.1.2 and B.3.2.3).

Discontinuation

The model permits treatment continuation beyond RECIST-defined disease progression in both the intervention and comparator arms. For NIVO+IPI and sunitinib, estimates of time to treatment discontinuation are derived from time to discontinuation (TTD) data from the CheckMate 214 trial. The TTD data for pazopanib is estimated from a non-inferiority trial (the COMPARZ trial) comparing pazopanib with sunitinib as first-line treatment of advanced RCC. An additional 5-year treatment discontinuation rule is applied to the NIVO+IPI arm in the company model as per expert clinical opinion received by the company.

5.2.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and personal social services (PSS). In line with NICE's Guide to the Methods of Technology Appraisal,[94] the analysis excludes out-of-pocket expenses, carer costs and productivity costs. The cycle length is 1 week and the time horizon is set at 40 years, assuming a 100-year life expectancy. Both costs and outcomes are discounted at 3.5% per annum, and a half-cycle correction is not used.

5.2.7 Treatment effectiveness and extrapolation in the base case

The company economic model relies on patient-level data from the CheckMate 214 trial. The follow-up period in this trial was shorter than the required length of the economic evaluation, which is equivalent to a lifetime. Extrapolation of the OS, PFS and TTD data from the Checkmate 214 trial was therefore necessary to enable a partitioned survival method to be used. Extrapolations involved identification of suitable parametric survival models for OS, PFS and TTD data.

Overall survival

The company generated a log-cumulative hazard plot to determine whether the PH assumption was valid for patient-level data from the CheckMate 214 trial. The Grambsch-Therneau test used by the company indicated the PH assumption holds for OS in the intermediate/poor risk population. However, the company assumed non-proportionality because there was an overlap of the log-cumulative hazards, and separation of the Kaplan Meier (K-M) and log-cumulative hazard curves after 3 months. Clinical opinion also indicated a plausible underlying biologic mechanism to support non-proportionality: NIVO+IPI contains two immunotherapeutic agents with different mechanism of action while sunitinib is a VEGFR-TKI. Survival analyses used in the model were therefore stratified by treatment arm because of the assumption of non-proportionality.

The company fitted seven parametric models to the CheckMate 214 trial data. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit values were initially used to identify the survival model with the best statistical fit. The preferred model was however chosen primarily on clinical plausibility, given the immaturity of the CheckMate 214 trial OS data and unavailability of long-term real-world evidence for NIVO+IPI. According to a clinical expert for the company, the 5-year survival for treatment with NIVO+IPI was 35% to 45% and was 15% to 20% for treatment with sunitinib. The company considered the log-logistic model to be consistent with clinical opinion (for NIVO+IPI and sunitinib) and with long-term real-world data from the sunitinib global expanded access programme by Gore et al 2015[60] (for sunitinib alone), and was therefore selected as the preferred model for NIVO+IPI and sunitinib.

The log-logistic model produces a flattening of the OS curve around 3 years, which the company attributes to immunotherapeutic survival benefit from treatment with immune checkpoint inhibitor either as a first-line or second-line treatment. The company notes that such long-term survival benefits have been modelled in a previous appraisal of nivolumab for previously treated advanced RCC (TA417). In TA417, clinical experts explained that there is a biological rationale for immunotherapeutic effect even after treatment stops, but only in durable responders. In the current CS, clinical advice to the company is that immunotherapeutic effect is plausible. The company also states that recent follow-up data from the CheckMate 025 trial[55] supports the assumption of immunotherapeutic survival benefit.

The proportion of durable responders in the company economic model was directly estimated from the CheckMate 214 trial for first-line NIVO+IPI (30.1%) and was indirectly estimated from the CheckMate 025 trial for second-line nivolumab (18.2%). The company modelled the

survival prospect in durable responders to be similar to that of the general population (CS, p87). The probability of the immunotherapeutic effect occurring with nivolumab either as first-line treatment or second-line treatment after sunitinib was estimated to be 50% in the company base case. The OS for patients receiving pazopanib was assumed to be the same as the OS for patients receiving Sunitinib.

Progression-free survival

According to the company, the log-cumulative hazard plot, the K-M plot, and the result of the Grambsch-Therneau correlation test suggest that the PH assumption is not valid for PFS. Seven standard parametric models and six spline-based models were fitted to the CheckMate 214 trial K-M patient-level data. Goodness of fit was assessed visually and also using the AIC and BIC statistics. Spline 2-knot hazard and spline 1-knot hazard models were the preferred models for treatment with NIVO+IPI and sunitinib respectively in the base case according to AIC statistics. The PFS for pazopanib in the company's base case was assumed to be equivalent to the PFS for sunitinib.

Time to treatment discontinuation

With a median TTD of 7.4 months and 6.2 months for NIVO+IPI and sunitinib respectively, the TTD data from the CheckMate 214 trial required extrapolation to estimate lifetime TTD across treatment arms. The company concluded that the assumption of PH was violated following its assessment of the log-cumulative hazard plot and application of the Grambsch-Therneau correlation test. Standard parametric models and six spline-based models were fitted to the CheckMate 214 trial data, stratified by treatment arm. Goodness of fit was assessed visually against the K-M data using the AIC and BIC statistics, and clinical opinion. Clinical advice to the company was that treatment would continue until the risk-benefit ratio was no longer tenable. [redacted] was chosen as the preferred model for each arm, as its prediction [redacted].

A HR of 0.95 was applied as a HR to the sunitinib TTD curve in the company model to derive TTD for pazopanib. The ratio was obtained from the COMPARZ non-inferiority trial, which reported a greater median treatment duration for pazopanib than sunitinib (8.0 months versus 7.6 months respectively). Additionally, a 5-year treatment discontinuation rule was applied to the NIVO+IPI arm in the company model as per expert clinical advice to the company. The maximum TTD for sunitinib and pazopanib, from extrapolation of the CheckMate 214 TTD data, is less than 5 years so no additional discontinuation rule was applied. The TTD curve for treatment with nivolumab is truncated at 5 years in the company base case as the company assumes prolonged IV treatment places an extreme burden on people. The maximum TTD for treatment with sunitinib and pazopanib is less than 5 years so truncation was not applied.

5.2.8 Health-related quality of life

For the first 6 months of the CheckMate 214 trial, the EQ-5D-3L questionnaire was administered to patients on Day 1 of Week 1 of each 6-week study cycle and on Day 1 of Week 4 of each study cycle. The questionnaire was completed again at the first two follow-up visits (approximately 30 days and approximately 114 days after the last dose). Thereafter, the questionnaire was completed every 3 months for the first 12 months, then every 6 months until the last follow-up visit. The UK EQ-5D-3L tariff was used to estimate utility values from the questionnaire responses.

The company used regression analyses to estimate the utility increment or decrement associated with some characteristics of intermediate/poor risk participants in the CheckMate 214 trial: (i) treatment received, (ii) treatment status and (iii) disease status. The regression analyses took the form of a mixed-effect model where utility was the dependent variable and unique identifiers for individuals were used as random effects to account for repeated measures. Seven model specifications with various combinations of the characteristics and their interaction terms were explored. The best-fitting model was assessed using the AIC. The final model estimated EQ-5D-3L utility scores as a function of treatment received, treatment status and the interaction between these variables.

The company conducted systematic literature searches to identify HRQoL studies. However, none of the studies evaluated treatment with NIVO+IPI in a UK-based population. The company states the HRQoL estimation approach described in the CS is similar to that used in a previous study of nivolumab for previously treated advanced RCC, the CheckMate 025 trial. The company states that although the CheckMate 025 trial applied the estimation approach in the ITT population (favourable, intermediate and poor risk), a comparison of the HRQoL data from the CheckMate 214 and CheckMate 025 trials shows that the direction and size of the EQ-5D-3L estimates are consistent.

For patients receiving first-line treatment, the company used health state utility values from the best-fitting utility mixed-effect model derived from the CheckMate 214 trial. Health state utility values for patients on second-line treatment were from the best-fitting mixed-effect model from the CheckMate 025 trial.

Impact of treatment discontinuation and disease progression on health state utility

The result of the regression analysis suggests that treatment discontinuation has significant negative consequences for health state utility, which the company states is consistent with expectations. The company further concludes that disease progression is not an independent

predictor of utility given its correlation with treatment discontinuation as shown by the data from the CheckMate 214 trial.

Impact of treatment type progression on health state utility

Compared to treatment with NIVO+IPI, the company concludes that treatment with sunitinib or pazopanib is associated with a lower utility score even after controlling for the interaction between treatment arm and treatment status. The company highlights that this result is consistent with the finding from TA417 where treatment the intervention (nivolumab) was associated with better patient EQ-5D-3L utility than treatment with the comparator (everolimus) in patients with previously advanced RCC. Table 19 shows the health state utility estimates from the CheckMate 214 and CheckMate 025 trials while Table 20 shows the health state utility values in the company economic model.

Table 19 Economic model health state values implied by CheckMate 214 EQ-5D-3L data, and health state values used in TA417 based on CheckMate 025 EQ-5D-3L data

Health state utility score	Trial arms	
CheckMate 214 (intermediate and poor risk)	**NIVO+IPI**	**Sunitinib**
PFS On 1LTx, PPS On 1LTx	0.793	0.751
PFS Off 1L Tx, PPS Off 1LTx	0.719	0.699
CheckMate 025 (TA417) (favourable, intermediate and poor risk)	**Nivolumab**	**Everolimus**
PFS On 2L Tx, PFS Off 2LTx	0.798	0.762
PPS On 2L Tx, PPS Off 2LTx	0.728	0.697

1L=first-line; EQ-5D-3L=EQ-5D 3-Level questionnaire; PFS=progression-free survival; PPS=post-progression survival; Tx=treatment
Source: CS, Table 29

Table 20 Summary of utility values for the company cost-effectiveness analysis

Health state utility score	Trial arms	
	NIVO+IPI	**Sunitinib or Pazopanib**
PFS On 1LTx, PPS On 1LTx	0.793	0.751
PFS Off 1L Tx, PPS Off 1LTx	0.719	0.699
PPS Off 1LTx receiving 2L Tx (nivolumab)	0.798	0.798
PPS Off 1LTx receiving 2L Tx (axitinib or cabozantinib)	0.762	0.762

1L=first-line; 2L=second-line; PFS=progression-free survival; PPS=post-progression survival; Tx=treatment
Source: CS, Table 33

Impact of adverse events on health state utility

Further utility adjustments are not made to account for AEs in the base case analyses as the company assumes that the HRQoL effects of TRAEs are inherently captured by the health state utilities. The company states that this assumption is consistent with the NICE appraisal committee-preferred analysis in TA417 (see Section B.3.4.3 of the CS). Nonetheless, the company explored the impact of TRAE disutility decrements in a scenario analysis (see Section B.3.8.3 in the CS).

5.2.9 Resources use and costs

Drug costs

Estimates of the quantity of nivolumab, ipilimumab and sunitinib used per patient per week are derived from the CheckMate 214 trial data. Data from a previous appraisal (TA215) were used to provide an estimate of the quantity of pazopanib used. The resource use estimates for nivolumab accounted for wastage, patient weight and adherence to medication. The estimates for sunitinib and pazopanib accounted for adherence.

PAS discounts were applied to list prices for nivolumab, ipilimumab, sunitinib and pazopanib in the base case analyses. Both nivolumab and ipilimumab are administered via IV infusion and therefore an additional treatment administration cost of £310 per dose was incurred. No vial sharing was assumed for NIVO+IPI in the base case. Details of drug costs is presented in Table 34 of the CS and reproduced in Table 21 of this ERG report.

Table 21 Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week for intervention and active comparators (list prices)

Drug	Dosing regimen	Cost per vial/pack (£)	Vial size / tablets per pack	Vials / tablets per admin	Proportion of dose received	Total cost per week*
Nivolumab	4x 3mg/kg Q3W IV, then 3mg/kg Q2W IV	1,097.00	100mg	1.64	[redacted]	[redacted]
		439.00	40mg	2.01		
Ipilimumab	4x 1mg/kg Q3W IV	15,000.00	200mg	0.02	[redacted]	[redacted]
		3,750.00	50mg	1.98		
Pazopanib	800mg oral daily	1,121.00	30 x 400mg	2.00	86%	£449.89
		560.50	30 x 200mg	4.00		
Sunitinib	50mg oral daily, 4 weeks on, 2 weeks off	3,138.80	28 x 50mg	1.00	97%	£674.84
		1,569.40	8 x 25mg	2.00		
		784.70	28 x 12.5mg	4.00		

IV=intravenous; Q2W=once every 2 weeks; Q3W=once every 3 weeks; *=although costs in the table are provided by week, the model costs nivolumab and ipilimumab by administration, i.e. a single cost is applied every 2 or 3 weeks
† This value was updated by the company to [redacted] after it identified a calculation error
Source: Adapted from CS, Table 34.
Note: where there are discrepancies between the CS and the company model, figures in this table reflect those used in the company model

Subsequent treatments

[redacted] in the CheckMate 214 trial. Clinical advice to the company states that it is likely that all patients failing sunitinib will go on to receive subsequent therapy, whereas the proportion would be 60% for patients in the NIVO+IPI arm. In the model base case, the company assumes that 60% and 80% of people treated with NIVO+IPI and sunitinib respectively will receive subsequent therapy (*** [redacted] 22).

[redacted] 22

Subsequent treatment received	Received in CheckMate 214		Clinical opinion	
	[redacted]	[redacted]	NIVO+IPI	Sunitinib
Nivolumab	[redacted]	[redacted]	0.0%	60.0%
Sunitinib	[redacted]	[redacted]	0.0%	0.0%
Pazopanib	[redacted]	[redacted]	0.0%	0.0%
Axitinib	[redacted]	[redacted]	30.0%	0.0%
Cabozantinib	[redacted]	[redacted]	30.0%	20.0%
Everolimus	[redacted]	[redacted]	0.0%	0.0%

Source: CS, adapted from Tables 38 and 39

Clinical advice received by the company (CS, p125) suggests that the distribution of subsequent therapies from the CheckMate 214 trial is not reflective of current clinical practice in the UK, and that second-line therapy would be between axitinib, cabozantinib and nivolumab.

For patients treated with NIVO+IPI, the expert advice received by the company (CS, p125) is that retreatment with nivolumab is not an option based on current guidelines. The company interprets the advice to mean subsequent therapy after NIVO+IPI is evenly split between axitinib and cabozantinib. For sunitinib, clinical opinion to the company is that subsequent treatment with another VEGFR-TKI is unlikely and describe cabozantinib as a potent but toxic drug. The company also considers that axitinib is a less toxic option than cabozantinib. In summary, [redacted]

[redacted]. For each drug, unit costs sourced from the Monthly Index of Medical Specialities (MIMS) were applied to dosing regimens to derive the costs per model cycle as shown in . The company applied PAS discount to the list price for treatment with nivolumab in the second-line setting. List prices without discounts are used for axitinib and cabozantinib. The full cost details for subsequent therapies is presented in Table 40 of the CS.

Table 23. The company applied PAS discount to the list price for treatment with nivolumab in the second-line setting. List prices without discounts are used for axitinib and cabozantinib. The full cost details for subsequent therapies is presented in Table 40 of the CS.

Table 23 Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week for subsequent therapies

Drug	Dosing regimen	Cost per vial/pack (£)	Vial size / tablets per pack	Vials / tablets per admin	Proportion of dose received	Total cost per model cycle (£)
Nivolumab	3mg/kg Q2W IV	439.00	40mg	6.00	[redacted]	[redacted]
Sunitinib	50mg daily orally, 4 weeks on, 2 weeks off	3,138.80	28 x 50mg	1.00	[redacted]	[redacted]
Pazopanib	800mg daily orally	1,121.00	30 x 400mg	2.00	[redacted]	[redacted]
Axitinib	5mg twice daily orally	3,517.00	56 x 5mg	1.00	[redacted]	[redacted]
Cabozantinib	60mg daily orally	5,143.00	30 x 60mg	1.00	[redacted]	[redacted]
Everolimus	10mg daily orally	2,673.00	30 x 10mg	1.00	[redacted]	[redacted]

IV=intravenous; Q2W=once every 2 weeks
Source: Adapted from CS, Table 40

Resource use by health state

Base case resource use and unit cost estimates attributed to disease management are shown in Table 24. Resource use assumptions used in two previous RCC technology appraisals (TA333 and TA417) were used in the model. Unit costs were obtained from the 2015/2016[9] and 2016/2017[10] NHS Reference Costs and the 2015[11] and 2017[12] Personal and Social Services Research Unit (PSSRU) costs. Unit costs in the company model are in 2016/2017 price base year. Unit costs from earlier price years are inflated to the base year[12].

Table 24 Resource use and costs associated with model health states

Health state	Resource	Frequency per week	Cost (£)
PFS	GP visit	0.250	£32.00
	CT scan	0.080	£142.99
	Blood test	0.250	£3.06
	Total		**£20.68**
PPS	GP visit	0.250	£32.00
	CT scan	0.380	£67.04
	Blood test	7.000	£5.46
	Total		**£71.38**
Terminal care	Community and acute care (8 week package)	0.125	£6,353.01
	Total		**£794.13**

CT=computed topography; GP=general practice; PFS=progression-free survival; PPS=post-progression survival
Source: Adapted from CS, Table 36 and End-of-Life cost section

Adverse event costs

The NHS cost implications for grade 3/4 TRAEs experienced by at least 15% of participants in either arm of the CheckMate 214 trial are included in the company base case analyses. The unit costs for each TRAE were sourced from previous appraisals of RCC. Next, the unit costs were applied to cycle event probabilities from the CheckMate 214 trial to produce AE cycle costs of £4.24 and £15.21 for NIVO+IPI and sunitinib respectively. The company assumed that the TRAEs cost for pazopanib was similar to sunitinib. A summary of the costs associated with TRAEs is presented in Table 25. Full details are available in Table 37 of the CS.

Table 25 Costs associated with TRAEs

Adverse event (grade 3 to 4)	Cost per episode	Source
Anaemia	£280.03	NHS reference cost (2016-17)
Asthenia	£659.11	NHS reference cost (2016-17); PSSRU (2017)
Diarrhoea	£788.25	NHS reference cost (2015-16); PSSRU (2017)
Decreased appetite	£617.11	NHS reference cost (2016-17)
Dysgeusia	£617.11	NHS reference cost (2016-17)
Fatigue	£659.11	NHS reference cost (2016-17); PSSRU (2017)
Hypertension	£859.78	NHS reference cost (2016-17); PSSRU (2017)
Hypothyroidism	£659.11	NHS reference cost (2016-17); PSSRU (2017)
Lipase increase	£280.03	NHS reference cost (2016-17)
Mucosal inflammation	£617.11	NHS reference cost (2016-17)
Nausea	£788.25	NHS reference cost (2015-16); PSSRU (2017)
Palmar-plantar erythrodysesthesia syndrome	£617.11	NHS reference cost (2016-17)
Pruritus	£617.11	NHS reference cost (2016-17)
Rash	£617.11	NHS reference cost (2016-17)
Stomatitis	£617.11	NHS reference cost (2016-17)
Thrombocytopenia	£280.03	NHS reference cost (2016-17)
Vomiting	£788.25	NHS reference cost (2015-16); PSSRU (2017)

PSSRU=personal and social services research unit
Source: Adapted from CS, Table 37

5.2.10 Cost effectiveness results

Base case results

Table 26 shows the pairwise base case incremental cost effectiveness ratios (ICERs) per QALY gained between treatment with NIVO+IPI versus its comparators. Table 27 shows the fully incremental cost effectiveness results for treatment with NIVO+IPI, sunitinib and pazopanib. PAS discounts are applied to nivolumab ([redacted]), ipilimumab ([redacted]), sunitinib (first cycle free) and pazopanib (12.5%) in the base case.

Table 26 Base case pairwise incremental cost effectiveness results – with PAS prices for NIVO+IPI and sunitinib

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (NIVO+IPI versus comparators)
				Cost	LYG	QALYs	
NIVO+IPI	[redacted]	8.04	4.43				
Sunitinib	[redacted]	4.53	2.68	£50,499	3.51	1.75	£28,865
Pazopanib	[redacted]	4.52	2.68	£50,423	3.51	1.75	£28,819

LYG=life year gained; QALY=quality adjusted life year
Source: adapted from CS, Table 44

Table 27 Base case fully incremental cost effectiveness results – with PAS prices for NIVO+IPI and sunitinib

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Inc. cost per QALY gained	Fully inc. cost per QALY gained
				Cost	LYG	QALYs		
Sunitinib	[redacted]	4.53	2.68					
Pazopanib	[redacted]	4.52	2.68	£76	-0.01	0.00	-£451,412	Strictly dominated
NIVO+IPI	[redacted]	8.04	4.43	£50,500	3.51	1.75	£28,865	£28,865

Inc=incremental; LYG=life year gained; QALY=quality adjusted life year; Inc=incremental
Source: adapted from CS, Table 45

5.2.11 Sensitivity analyses

Deterministic sensitivity analyses

Results of one-way sensitivity analyses (OWSA) show that TTD curve parameters for NIVO+IPI, proportion of people on subsequent therapy, proportion of people on first-line therapy benefiting from immunotherapeutic effect and the proportion of scheduled first-line doses received have the greatest impact on the size of the ICER per QALY gained as shown in ***[redacted]2 and ***[redacted]3.

[redacted]2[redacted]ICER=incremental cost-effectiveness ratio; IO=immune-oncology; OS=overall survival; OWSA=one-way sensitivity analysis; TOT=time on treatment; TTD=time to treatment discontinuation
Source: CS, Figure 36

[redacted]3[redacted]

ICER=incremental cost-effectiveness ratio; IO=immune-oncology; OS=overall survival; OWSA=one-way sensitivity analysis; TOT=time on treatment; TTD=time to treatment discontinuation
Source: CS, Figure 37

Probabilistic sensitivity analysis

The company varied a large number of input parameters in its probabilistic sensitivity analysis. ***[redacted]4 show the uncertainty around the estimated mean cost per QALY difference between

treatment with NIVO+IPI versus treatment with sunitinib and pazopanib respectively. The mean probabilistic ICER of £30,886 per QALY gained for NIVO+IPI versus sunitinib was higher than the deterministic ICER of £28,865 per QALY gained. In the incremental probabilistic analysis, pazopanib is marginally more effective and marginally more expensive than sunitinib (ICER= £423,335 per QALY gained). However, the presence of another intervention, NIVO+IPI that is markedly more effective and marginally more expensive than pazopanib (ICER=£30,886) means NIVO+IPI extendedly dominates pazopanib. In the incremental deterministic analysis however, sunitinib strictly dominated pazopanib by being more effective and cheaper. The company states that the difference between the result of the deterministic and probabilistic incremental analyses is because the [redacted]. The phenomenon also partly explains the higher ICER per QALY gained for sunitinib. Overall, the probability of treatment with NIVO+IPI being the most cost effective treatment option at a willingness-to-pay threshold of £30,000 per QALY was [redacted].

[redacted]4 [redacted]ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; PSA=probabilistic sensitivity analysis; WTP=willingness-to-pay
Source: CS, Figure 33

[redacted]ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; PSA=probabilistic sensitivity analysis; WTP=willingness-to-pay
Source: CS, Figure 34

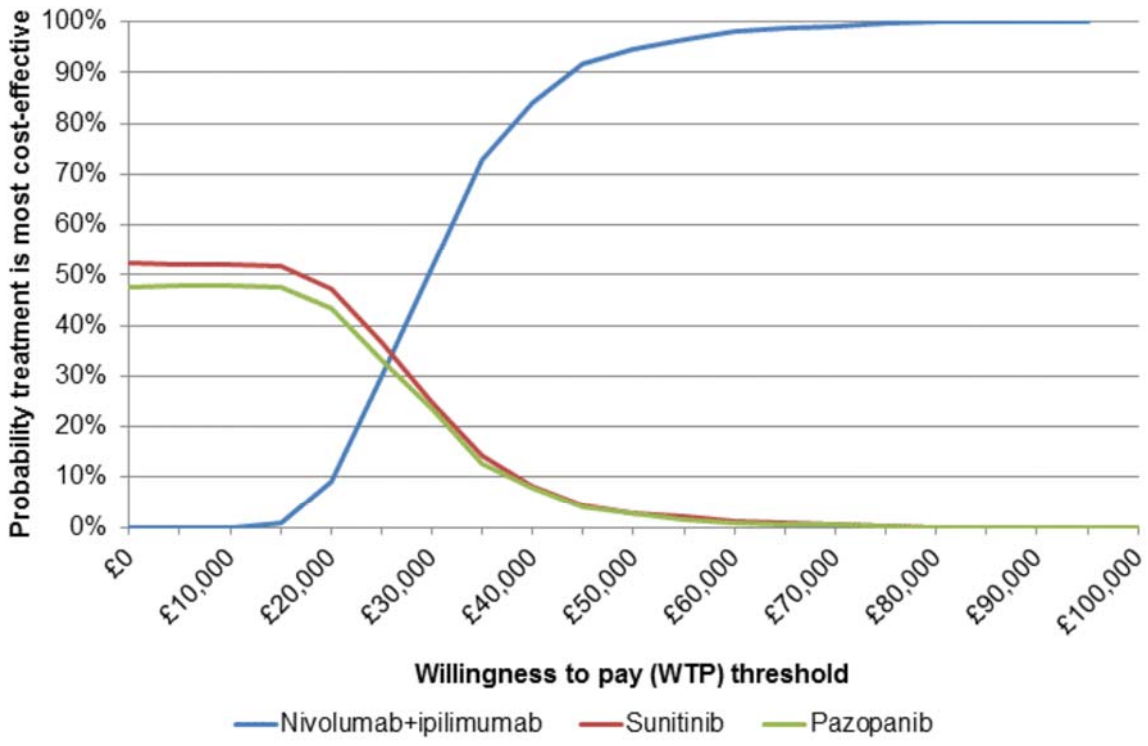

Figure 6 Cost effectiveness acceptability curve of treatment with NIVO+IPI vs sunitinib and pazopanib

Source: CS, Figure 35[redacted]

5.2.12 Scenario analyses

The company notes that the results of the scenario analyses are largely robust to changes in most parameters. The main exceptions are: changes to the discount rate, immunotherapeutic

effect from immune checkpoint inhibitors, the proportion of people receiving subsequent therapy, treatment stopping rule, and alternative assumption for OS. Selected results are shown in Table 28. Full details of the scenario analyses are presented in the CS, Table 48.

Table 28 Scenario analyses results

Description	Base case	Scenario analysis	NIVO+IPI vs sunitinib ICER	NIVO+IPI vs pazopanib ICER
Base case			£28,865	£28,819
Discount rate (costs and utilities)	3.5%	6.0%	£34,683	£34,657
		0.0%	£21,415	£21,358
Time horizon (years)	40	25	£30,402	£30,358
		30	£29,283	£29,237
OS fitted curve choice (NIVO+IPI and sunitinib)	Log-logistic	Log-normal	£26,442	£26,395
OS curve choice (dependence)	Independent	Dependent, log-logistic	£33,697	£33,643
PFS fitted curve choice (NIVO+IPI and sunitinib)	Spline 2 knots - hazard - gamma 1, Spline 1 knot - hazard - gamma 1	Spline 1 knot - odds - gamma 1	£27,768	£27,722
TTD fitted curve choice (NIVO+IPI and sunitinib)	[redacted]	[redacted]	£31,398	£31,367
Probability of durable responders on NIVO+IPI or nivolumab receiving long-term immunotherapy survival benefit	50%	0%	£34,371	£34,362
		100%	£25,432	£25,372
Dosing method	Weight-based	Hybrid dosing (240 Q2W)	£28,388	£28,342
		Hybrid dosing (480 Q4W)	£26,394	£26,348
		Flat dosing (240 Q2W)	£30,103	£30,056
		Flat dosing (480 Q4W)	£27,784	£27,737
Proportion of patients receiving subsequent therapy	60% NIVO+IPI, 80% sunitinib	100%	£31,697	£31,702
		0%	£33,882	£33,592
Adverse event disutilities applied from the literature	No	Yes	£28,869	£28,822
Treatment stopping rule	Yes, 5 years	Yes, 3 years	£25,574	£25,527
		No	£30,452	£30,406

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; Q2W=every 2 weeks; Q4W=every 4 weeks; QALY=quality adjusted life year; TTD=time to treatment discontinuation
Source: CS, adapted from Table 48

5.2.13 Model validation and face validity check

The company states that input from clinical experts was sought during the model development. Additionally, external health economists assessed the model for coding errors and validated the model.

5.3 ERG detailed critique of company economic model

5.3.1 Drummond checklist

Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	The overall survival data from CheckMate 214 was immature.
Were all the important and relevant costs and consequences for each alternative identified?	Partially	The number immune-mediated adverse events was identified, but the associated costs were not modelled
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Partially	The ERG considers the company's inclusion of immunotherapeutic OS benefit may overestimate the effectiveness of NIVO+IPI
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER was calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	The company undertook deterministic, scenario and probabilistic sensitivity analyses
Did the presentation and discussion of study results include all issues of concern to users?	Partially	The ERG considers further discussion on the discontinuation rule for NIVO+IPI would have been appropriate.

5.4 ERG critique of the company's economic model

5.4.1 Company model corrections

The ERG received notice during the analysis period that the company had identified an error in their base case model which affected the estimated cost of ipilimumab. Rectifying this error decreased the company's base case ICER by £797 to £28,068 per QALY gained for treatment with NIVO+IPI versus treatment with sunitinib and by £797 to £28,022 per QALY gained for treatment with NIVO+IPI versus treatment with pazopanib. The ERG has used the revised ICERs per QALY gained as the base case estimates throughout this section.

5.4.2 Key issues in the company model

The main issues in the company model are connected to the assumption of a long-term immunotherapeutic effect for treatment with NIVO+IPI in the first-line setting and with nivolumab in the second-line setting. These issues are around whether a long-term

immunotherapeutic effect exists; if it does exist, what form does it take; and how is the assumption of a long-term immunotherapeutic effect applied in the model.

The ERG considers there is considerable uncertainty surrounding the existence of any long-term survival effect for the treatment of advanced RCC with immunotherapy. The company does not clearly define what it considers to be a long-term immunotherapeutic effect on survival, which is fundamental to interpret the available trial evidence for treatment with nivolumab and ipilumumab. The company refers to the existence of 'survival plateaus' in the trial evidence and uses general population mortality rates to represent a long-term survival benefit in the submitted model. The ERG has reviewed the trial evidence for a long-term immunotherapeutic effect on survival in advanced RCC and advanced melanoma as referenced in the CS (from the Checkmate 003, CheckMate 010, CheckMate 025 and CheckMate 067 trials, and papers by the Schadendorf et al 2015[108] and Gore et al 2015[60]) and has concluded that the data do not support the company's modelling assumptions regarding long-term survival; since there is limited long-term evidence available and the evidence that exists, is not robust. The ERG's review of the evidence supporting a long-term immunotherapeutic effect for treatment with NIVO+IPI, and nivolumab and ipilmumab monotherapy, is presented in Section 5.4.3 of this ERG report.

The ERG also considers there is considerable uncertainty surrounding the form of any immunotherapeutic effect. First, since the company has assumed that a long-term immunotherapeutic can be modelled as a mortality risk equalling that of the general population, i.e., the company is assuming that a proportion of patients with advanced RCC will be cured of the disease. Clinical advice to the ERG is that, whilst cure (defined as a durable complete response) may be possible with immunotherapeutic treatments, such assumptions should be treated with extreme caution given the lack of long-term evidence available.

There is also considerable uncertainty surrounding the impact of a long-term immunotherapeutic effect on patient outcomes (i.e., how it is applied in the model). The company has modelled a long-term immunotherapeutic effect to affect OS in isolation and has not investigated the impact of an immunotherapeutic effect on any other outcome. This means that PFS, utility values and immune-mediated AEs are not explicitly modelled to link to the immunotherapeutic action of treatment with NIVO+IPI. However, the company explicitly assumes that a patient who benefits from a long-term immunotherapeutic effect also exhibits a durable response to treatment (defined with reference to the CheckMate 214 trial as 'ongoing response at the time of data cut-off'); this assumption is inherent in the company's argument for the existence of a long-term survival effect (e.g., CS, p60; CS, p61; CS, p87) and in the company's estimate of the proportion of patients who will benefit. If a long-term

immunotherapeutic effect is linked to durable response (durable response being a sub-category of PFS), then the ERG would expect to see that link modelled across all relevant outcomes. However, examination of the long-term trends currently evident in the PFS and OS K-M data from the CheckMate 214 trial do not suggest a strong link between PFS and long-term survival.

Finally, the company asserts that its modelling of a long-term survival benefit represents the assumption that OS rates for a specific proportion of patients treated with NIVO+IPI (and nivolumab in the second-line setting) match OS rates for the general population; that is, that a specific proportion of patients are cured of the disease but the remainder retain some mortality risk linked to advanced RCC. However, the way the company has implemented this assumption in the model results in OS matching general population OS for all patients who live for at least 7 years after beginning treatment with NIVO+IPI (or 14 years after beginning treatment with sunitinib); that is, that any patient treated with NIVO+IPI and living for at least 7 years will be cured of the disease and will no longer be at any risk from advanced RCC.

Other issues in the company model are also of concern: the immaturity of the data from the CheckMate 214 trial, which leads to uncertainty in the projection of OS in particular; the definition of PFS; the assumption of a stopping rule for treatment with NIVO+IPI; the method used to calculate utility values.

5.4.3 Long-term immunotherapeutic effect

The company's assumption of a long-term effect is based on its contention that a "survival plateau" is evident in the reported OS K-M data from a number of trials investigating treatment with ipilimumab or nivolumab for advanced RCC or melanoma (Table 29). The company does not explicitly define what constitutes a survival plateau, so the ERG has assumed it to mean either a) a portion of the survival curve that is flat or close to flat or b) a portion of the survival curve that indicates mortality rates are close to that of the general age-adjusted population. It is important to note that a totally flat OS curve represents zero risk of death from any cause, which the ERG considers to be implausible. A long, flat plateau can be evident in a K-M curve when the number of patients at risk diminishes quickly due to censoring, which leaves a population still under observation that is too small to allow detection of events even though a real risk of death still exists. Mortality rates close to the general age-adjusted mortality rates would indicate no additional risk from the disease of interest and that the patient has essentially been cured. All-cause mortality risk for the general UK population is around 0.7% annually at age 60, rising to 5% at age 80 and 16% at age 90.[109]

Long-term survival plateau in advanced RCC

To compare cumulative OS hazards, the ERG has digitised published K-M data from the trials of nivolumab monotherapy in advanced RCC that were referenced by the company (CheckMate 003, [110]CheckMate 010[111] and CheckMate 025[5]) and from an expanded global access trial of sunitinib (intermediate and poor risk groups only).[60] The ERG does not consider that these trials provide evidence of a survival plateau with close to zero mortality risk, nor do they provide robust evidence of mortality rates close to all-cause mortality rates.

The three CheckMate trials randomised previously treated patients, and the expanded access trial included a majority (78%) of previously treated patients, so the results of these trials should be interpreted with caution with reference to the current appraisal. It should also be noted that both the CheckMate 003 and CheckMate 010 trials included multiple nivolumab monotherapy dose regimens, which may influence the shape of the results shown in Figure 7.

Figure 7, Figure 8 and Figure 9 show that OS HRs appear to decrease over time to a greater or lesser extent in the CheckMate 003, CheckMate 010 and CheckMate 025 trials, and in the global extended access trial of sunitinib. This pattern is to be expected, as less fit patients will likely to die earlier than fitter patients and the patients left at risk will have lower mortality risk. However, mortality rates do not approach general mortality rates in any of these trials during the reported study period (Table 30).

Table 29 Overview of trials and studies used as evidence for long-term immunotherapeutic survival effect

Name	Disease	Design	Treatment arms	Population	Risk groups	Follow up (OS)
CheckMate 003[110]	RCC	Phase I N=34	Nivolumab 1mg/kg Q2W Nivolumab 10mg/kg Q2W	Previously treated ECOG≤2	NR	5 years
CheckMate 010[111]	RCC	Phase II N=168	Nivolumab 0.3mg/kg Q3W Nivolumab 2mg/kg Q3W Nivolumab 10mg/kg Q3W	Previously treated KPS≥70	MSKCC	5 years
CheckMate 025[55,112]	RCC	Phase III N=803	Nivolumab 3mg/kg Q2W Everolimus 10mg orally daily	Previously treated KPS≥70	MSKCC	3 years
Gore et al 2015[60]	RCC	Expanded access N= 4543	Sunitinib 50 mg per day, 4-weeks-on-2-weeks-off	Treatment naïve (22%) and previously treated (78%)	IMDC MSKCC	3 years
CheckMate 003[113]	Melanoma	Phase I N=107	Nivolumab 0.1mg/kg Q2W Nivolumab 0.3mg/kg Q2W Nivolumab 1mg/kg Q2W Nivolumab 3mg/kg Q2W Nivolumab 10mg/kg Q2W	Previously treated ECOG≤2	N/A	5 years
CheckMate 067[114]	Melanoma	Phase III N= 945	NIVO+IPI Nivolumab 3mg/kg Q2W (+ipilimumab placebo) Ipilimumab 3mg/kg Q3W (+nivolumab placebo)	Treatment naïve	N/A	3 years
Schadendorf pooled analysis[108]	Melanoma	3 x Phase I/II (N=180) 5 x Phase II (N=641) 2 x Phase III (N=790) 2 x observational (N=250) 1 x expanded access (N=2,985)	Ipilimumab (various doses)	Previously treated and treatment naive	N/A	Median follow up = 11 months Eight of 13 studies had at least 5 years minimum follow up

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky Performance Scale; MSKCC= Memorial Sloan Kettering Cancer Center; NR=not reported; Q2W=every 2 weeks; Q3W=every 3 weeks; RCC=renal cell carcinoma;

Table 30 Selected RCC trial mortality rates and general UK population mortality rate

Source	Last recorded event (a)	Average age at entry (b)	Age at last recorded event (a+b)	% male : % female	Annual mortality rate	
					End of trial K-M data+	Age- and sex- adjusted UK population
CheckMate 025	Nivolumab: 45 months Everolimus: 48 months	Nivolumab: 62 years Everolimus: 62 years	Nivolumab: 65.8 years Everolimus: 66.1 years	Nivolumab: 77%:23% Everolimus: 74%:26%	Nivolumab: 29.3% Everolimus: 28.2%	Nivolumab: 1.1% Everolimus: 1.2%
CheckMate 003 (RCC)	49 months	58 years	62.1 years	76% : 24%	12.8%	0.9%
CheckMate 010	49 months				22.7%	
Expanded access trial of sunitinb	Poor risk: 54 months Int risk: 64 months	59 years*	Poor risk: 63.5 years Int risk: 64.3 years	74% : 26%*	Poor risk: 25.2% Int risk: 10.2%	Poor risk: 0.9% Int risk: 1.0%

* Unknown for risk groups separately
+ Or final five data points, if final 12 months includes fewer than five points
Note: age-adjusted general UK population mortality rates do not go above 5% per year until the age of 80 for men and 82 for women
Source: Gore et al 2015[60]

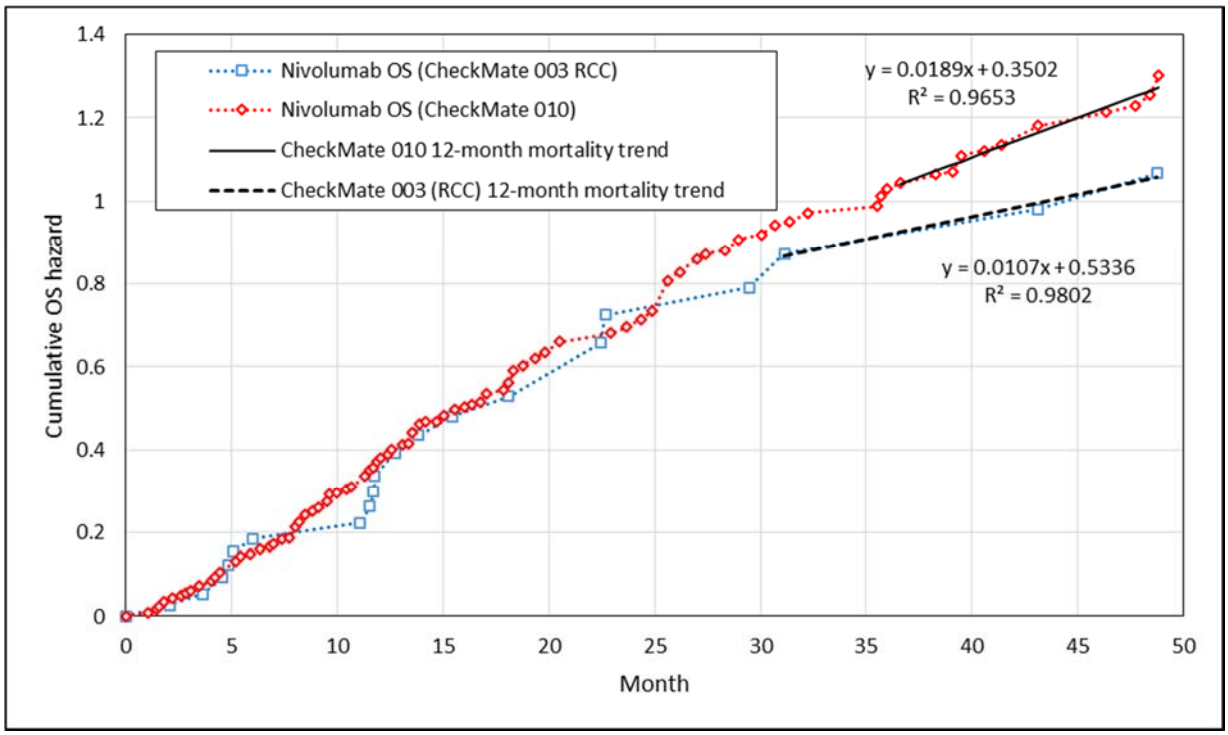

Figure 7 Cumulative OS hazard: nivolumab (CheckMate 003 RCC arm and CheckMate 010)

Source: digitised from McDermott et al 2015[110] and Plimack et al 2015[111]

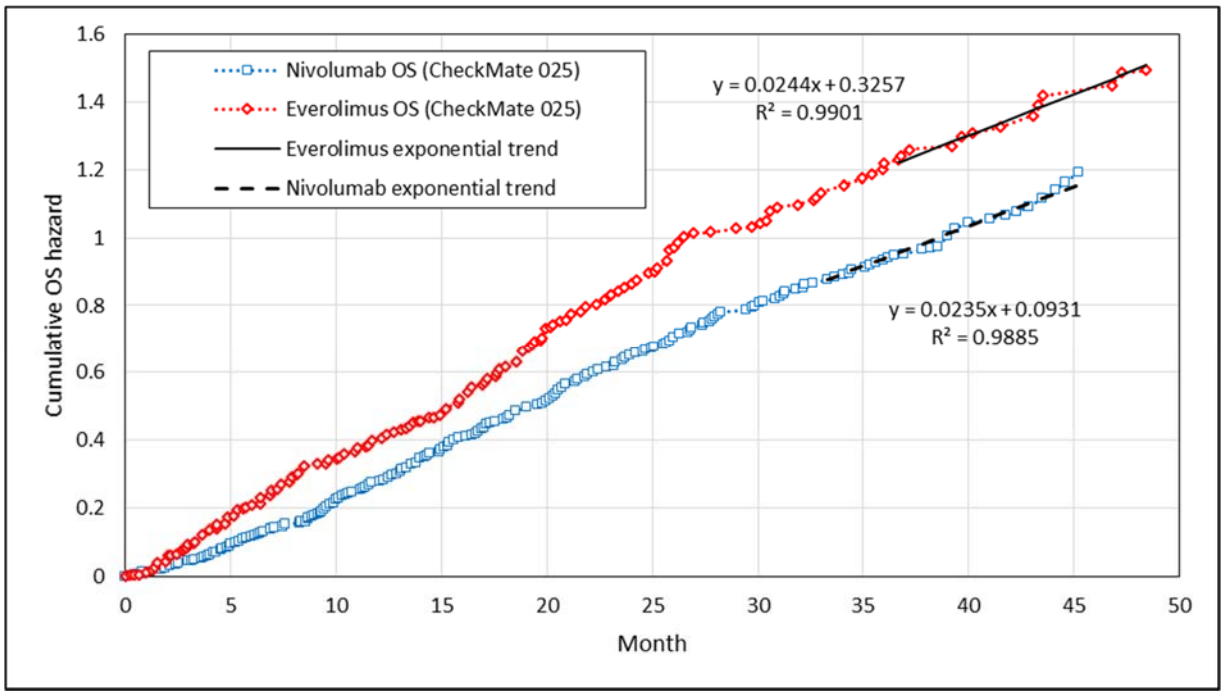

Figure 8 Cumulative OS hazard: nivolumab versus everolimus (CheckMate 025)

Source: digitised from Motzer et al 2015[5]

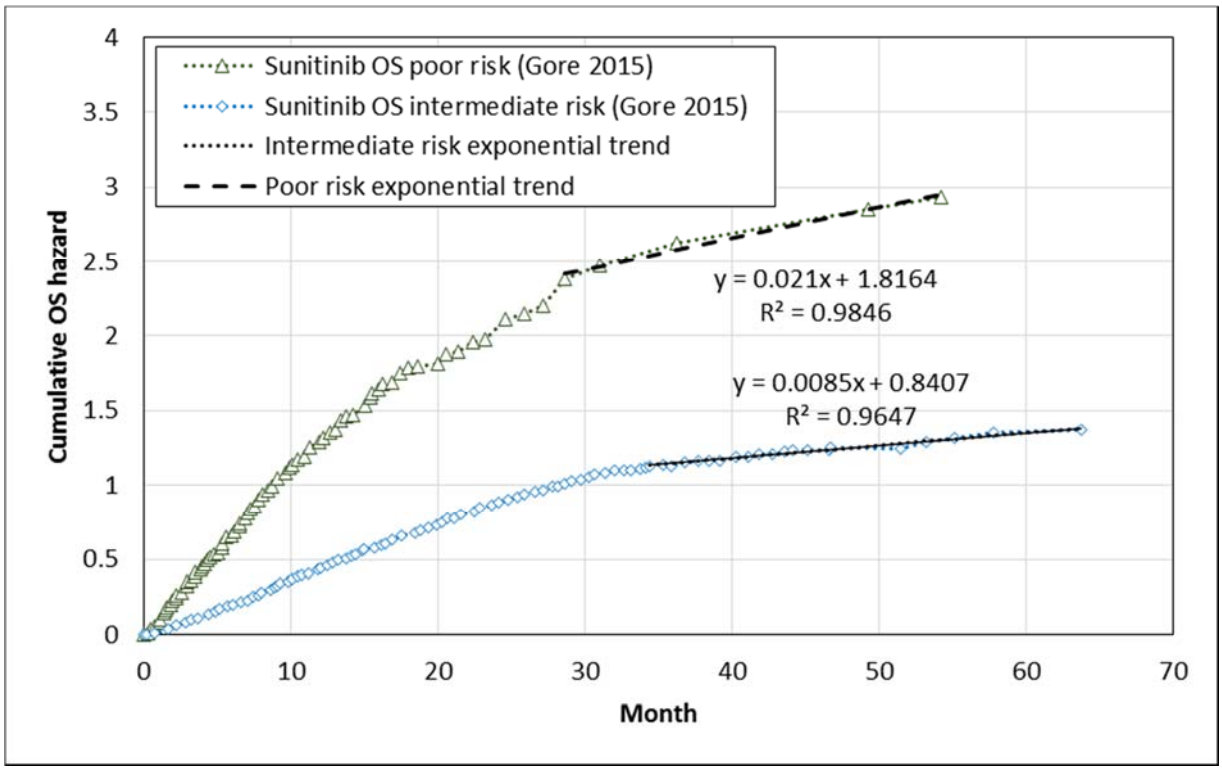

Figure 9 Cumulative OS hazard plot: sunitinib intermediate risk and poor risk groups (global expanded access trial)

Source: digitised from Gore et al 2015[60]

Long-term survival plateau in advanced melanoma

The ERG urges caution when drawing inferences from data for immunotherapeutic agents in other cancers. Clinical advice to the ERG notes that melanoma and RCC are biologically different diseases, so may not respond in the same way to the same treatment.

The company refers to OS evidence from the melanoma arms of the CheckMate 003 trial,[113] a pooled analysis of trials of treatment with ipilimumab in patients with advanced melanoma,[108] and to the CheckMate 067[114] trial of treatment with NIVO+IPI for advanced melanoma to further support its assumption of a long-term immunotherapeutic effect. The ERG's analysis of the evidence in treatment of advanced melanoma referred to in the CS does not indicate the presence of a flat survival curve. Although mortality risk appears to decline in each of the three studies considered, it does not approach general population mortality during the study period (Table 31).

Table 31 Selected melanoma trial mortality rates and general UK population mortality rate

Source	Last recorded event	Average age at entry	Age at last recorded event	% male : % female	Annual mortality rate	
					End of trial K-M data	Age- and sex-adjusted UK population
CheckMate 003 (Melanoma)	62 months	61 years	66.2 years	61%:39%	9.5%	1.1%
Schadendorf study	75 months	60 years*	66.3 years	65%:35%*	5.2%	1.1%
CheckMate 067	39 months	60 years	63.3 years	65%:35%	10.4%	0.9%

* Assumed equal to CheckMate 067 trial
Source: Schadendorf et al 2015[108]; Hodi et al 2016[113]; CheckMate 067[114]; ERG calculations; ONS 2014 to 2016 life table[109]

Figure 10 shows the cumulative hazards plots from the CheckMate 003 trial (melanoma arm), CheckMate 067 trial and pooled analysis of ipilimumab studies. All three indicate decreasing hazards over time, but none approach zero mortality risk during the trial period (represented by the slope of the linear trend at the end of the K-M data).

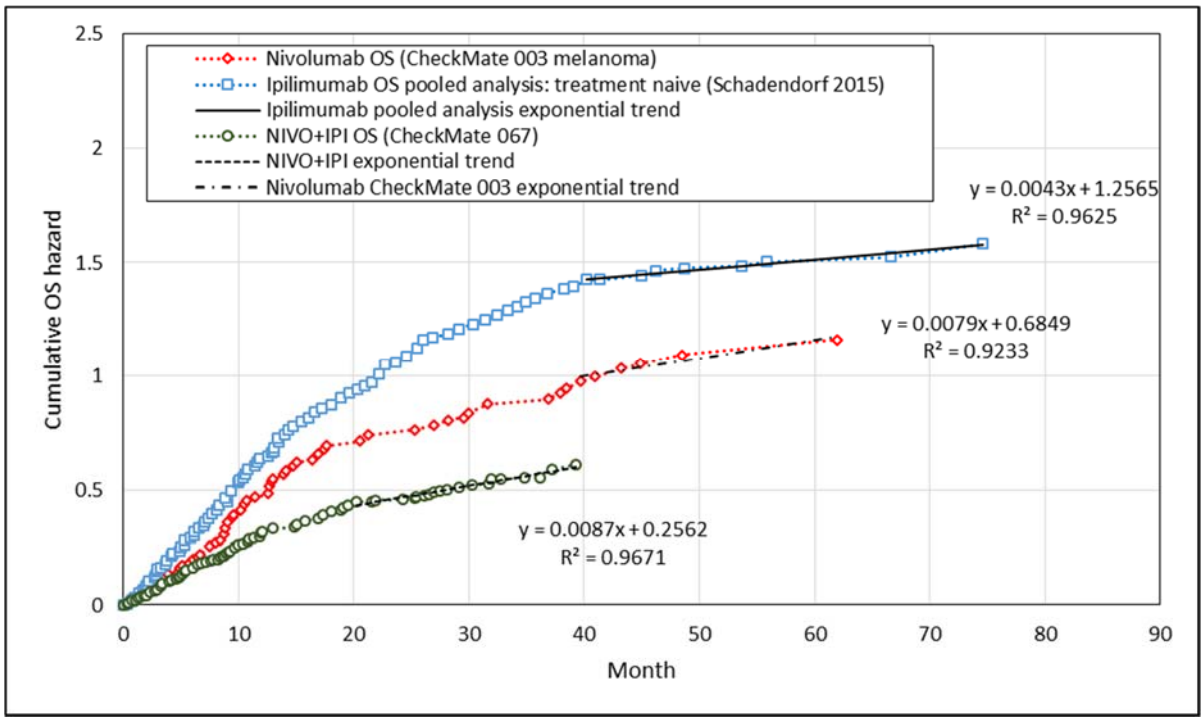

Figure 10 Cumulative OS hazards for immunotherapy in advanced melanoma: CheckMate 003 and pooled analysis

Source: Schadendorf et al 2015[108]; Hodi et al 2016[113]

Estimate of proportion of patients benefitting from immunotherapeutic effect

The proportion of patients who are assumed to achieve a long-term benefit from an immunotherapeutic effect is defined by the company as the proportion of 'durable responders' in the CheckMate 214 trial. Durable responders are defined by the company as those patients who achieved a response to treatment with NIVO+IPI in the CheckMate 214 trial (first-line setting) or to nivolumab in the CheckMate 025 trial (second-line setting) and were still responding at the time of the data cut. This definition yields an estimate of 30.1% in the first-line setting and 18.2% in the second-line setting.

The company's definition of patients who are assumed to benefit from an immunotherapeutic effect is linked to PFS, as durable response indicates that a patient has not yet progressed and therefore remains in PFS. However, the company does not link PFS to OS in its model. The company acknowledges in its response to an ERG clarification question (Question B4) that, "should an immunotherapeutic effect exist, and be predicted by durable response, it is likely to impact both PFS and OS." The company then explains that it is "uncertain as to what the extent of the PFS effect would be relative to OS" and considers that including an immunotherapeutic effect on OS alone to be a conservative approach.

Since any link between PFS and OS is uncertain and not modelled in the company's cost effectiveness analysis, the ERG considers that basing an estimate of the proportion of patients

who might benefit from an immunotherapeutic effect on the proportion of durable responders to also be uncertain at best. The company has investigated the effect of changing the proportion of patients who benefit from an immunotherapeutic survival effect by plus or minus 20% (36.0% [upper bound] or 24.2% [lower bound]for treatment with NIVO+IPI and 21.7% [upper bound] or 14.5% [lower bound] for treatment with sunitinib or pazopanib). This results in the company's ICERs per QALY gained for treatment with NIVO+IPI versus treatment with sunitinib ranging between £26,024 and £30,211, and the company's ICERs per QALY gained for treatment with NIVO+IPI versus treatment with pazopanib ranging between £25,972 and £30,179.

5.4.4 Outcomes by risk group

The ERG requested K-M data from the CheckMate 214 trial split by intermediate and poor risk groups from the company during the clarification process. The ERG reasoned that, given that patients with advanced RCC are routinely categorised into risk groups based on the number of certain prognostic factors they present with, membership of those risk groups might indicate different clinical outcomes that could be informative for modelling. The ERG acknowledges that the CheckMate 214 trial was not powered to assess differences in OS and PFS for the intermediate and poor risk groups separately. However, it can still be instructive to investigate the impact of clinical groupings that are expected to have an impact on mortality risk, since it may help explain the shape of the results for the combined group.

The intermediate/poor risk group in the CheckMate 214 trial comprises 79% intermediate risk patients and 21% poor risk patients in both the NIVO+IPI and sunitinib arms. As the majority of patients in the intermediate/poor risk group are considered to have intermediate risk, the outcomes for these patients will have the greatest influence on the overall results for the combined group.

Overall survival

Analysis of the OS K-M data split by risk group suggests [redacted] suggest that the response to treatment may be different in the two risk groups even though comparing the HRs for each group indicates no evidence of a difference.

[redacted]11

Source: Company clarification response B1

[redacted]12

Source: Company clarification response B1

The conflict between the conclusions of statistical and visual analysis of the OS data by risk group is the combined result of the immaturity of the data, the fact the trial was not powered to detect differences by risk group and because the PH assumption does not hold in the intermediate risk group (see Appendix 2, Sections 9.2.6 and 9.2.7, [redacted]38 and [redacted]39).

The violation of the PH assumption invalidates the HR calculation and thus adds further uncertainty to the size of the OS treatment effect for the intermediate-risk group.

Progression-free survival

Analysis of the PFS K-M data from the CheckMate 214 trial used by the company to inform its base case PFS model (IRRC assessed, primary definition) [redacted]

[redacted]13[redacted]

Source: Company clarification response B1

[redacted]14[redacted]

Source: Company clarification response B1

In the ERG's preferred PFS analysis for the economic evaluation (investigator-assessed secondary definition: see Section 5.5.3 of this ERG report), [redacted]42[redacted]42[redacted]42[redacted]42
[redacted]42[redacted]42[redacted]42[redacted]42[redacted]42[redacted]42[redacted]42[redacted]42
[redacted]42[redacted]42[redacted]42.

[redacted]15

Source: Company clarification response question B1

[redacted]16

Source: Company clarification response question B1

The PH assumption is violated for both risk groups in both the IRRC-assessed primary definition of PFS and the investigator-assessed secondary definition of PFS (Appendix 2, Section 9.2.10 and 9.2.11, [redacted]42 and [redacted]43), which undermines the HR calculation and adds uncertainty to assessment of the PFS treatment effect.

5.4.5 Equality of outcomes assumption for sunitinib and pazopanib

The company has assumed that treatment with pazopanib yields the same OS, PFS, AE and utility outcomes as treatment with sunitinib. The ERG considers there to be insufficient evidence of a statistically significant difference in OS and PFS between treatment with sunitinib and treatment with pazopanib based on the results on the COMPARZ trial (Section 4.7.7, Table 14 and Table 15). Clinical advice to the ERG is also that OS and PFS are widely considered to be similar for both treatments.

The ERG acknowledges there may be a bias against treatment with pazopanib in the company model as a result of the assumption that AEs and utility values are the same for treatment with sunitinib and treatment with pazopanib, since clinical advice to the ERG is that pazopanib is

generally considered to be a more tolerable treatment than sunitinib. The ERG notes that the company has performed a scenario analysis to investigate this potential bias, which has a minor impact on the resulting ICERs per QALY gained. The ERG has investigated the impact of using a larger differential between utility values for treatment with sunitinib and treatment with pazopanib than is used in the company scenario; that is, the ERG has assumed that with utilities for treatment with pazopanib are equal to utilities for treatment with NIVO+IPI. Assuming that utility values for treatment with pazopanib are equal to those for treatment with NIVO+IPI results in a difference of £1,413 per QALY gained between the two treatments when using the ERG's revised base case assumptions (Section 5.6).

The ERG has maintained the company's assumption that OS, PFS, AE and utility outcomes are equal for treatment with sunitinib and treatment with pazopanib, with the caveat that this assumption may result in some bias against treatment with pazopanib.

5.4.6 Overall survival: NIVO+IPI and sunitinib

The ERG has identified two major issues in the company's modelling of OS: implausible mortality rates associated with the modelling of no immunotherapeutic effect, related to the use of a log-logistic curve; and implausible mortality rates associated with the modelling of a long-term immunotherapeutic effect, related to a flawed application of general population mortality rates.

The company incorporates the assumption of an immunotherapeutic effect on OS via a mixed model. The mixed model comprises survival projections for two scenarios: one with no assumption of a long-term survival effect; and one including the assumption that general population mortality rates are applicable for patients treated with NIVO+IPI when OS reaches 30%, when OS reaches 7.9% for treatment with sunitinib and 7.8% with pazopanib. The figures for treatment with sunitinib and pazopanib represent the proportion of patients who are expected achieve a long-term survival benefit from second-line treatment with nivolumab (18.2%) out of those patients who are treated with nivolumab in the second-line setting (60%) out of those patients who are eligible for second-line treatment (72% for treatment with sunitinib and 71% for treatment with pazopanib). The two survival scenarios are then combined at a weight of 50% each to represent a 50% likelihood of the existence of an immunotherapeutic effect.

The two component OS curves are shown in Figure 17 (no immunotherapeutic effect) and Figure 18 (immunotherapeutic effect), and the combined base case OS curves are shown in Figure 19.

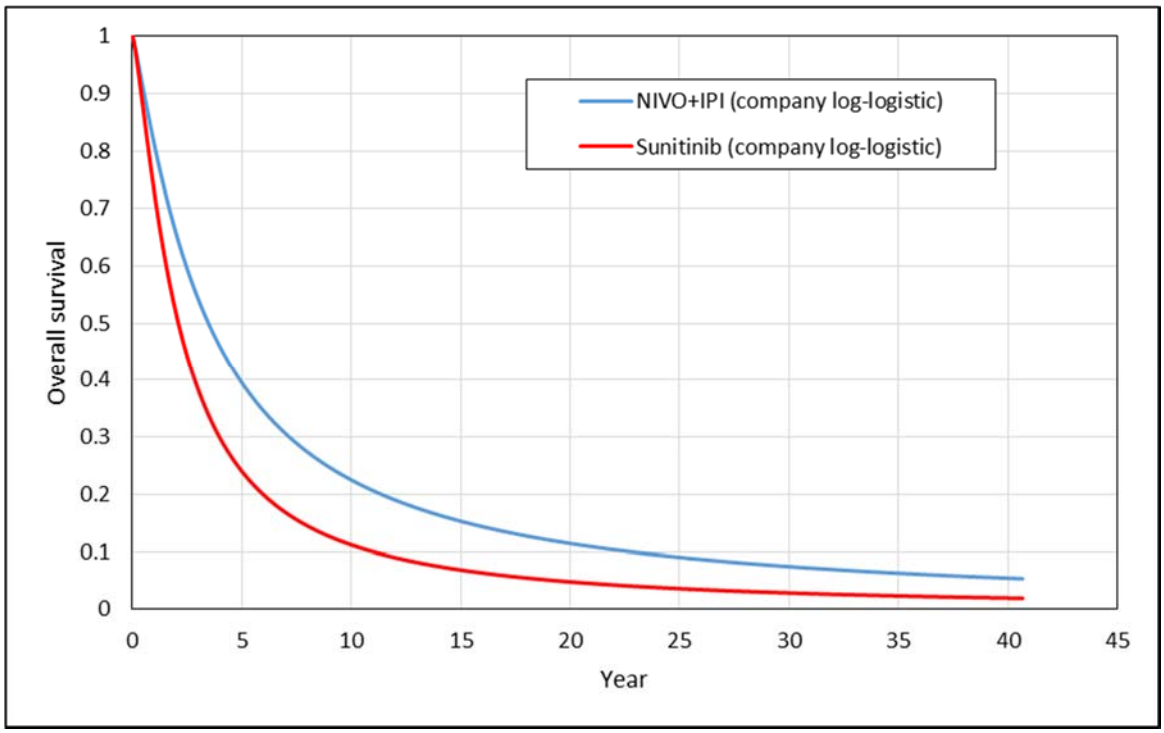

Figure 17 Company log-logistic OS curves (no immunotherapeutic effect)

Source: company model

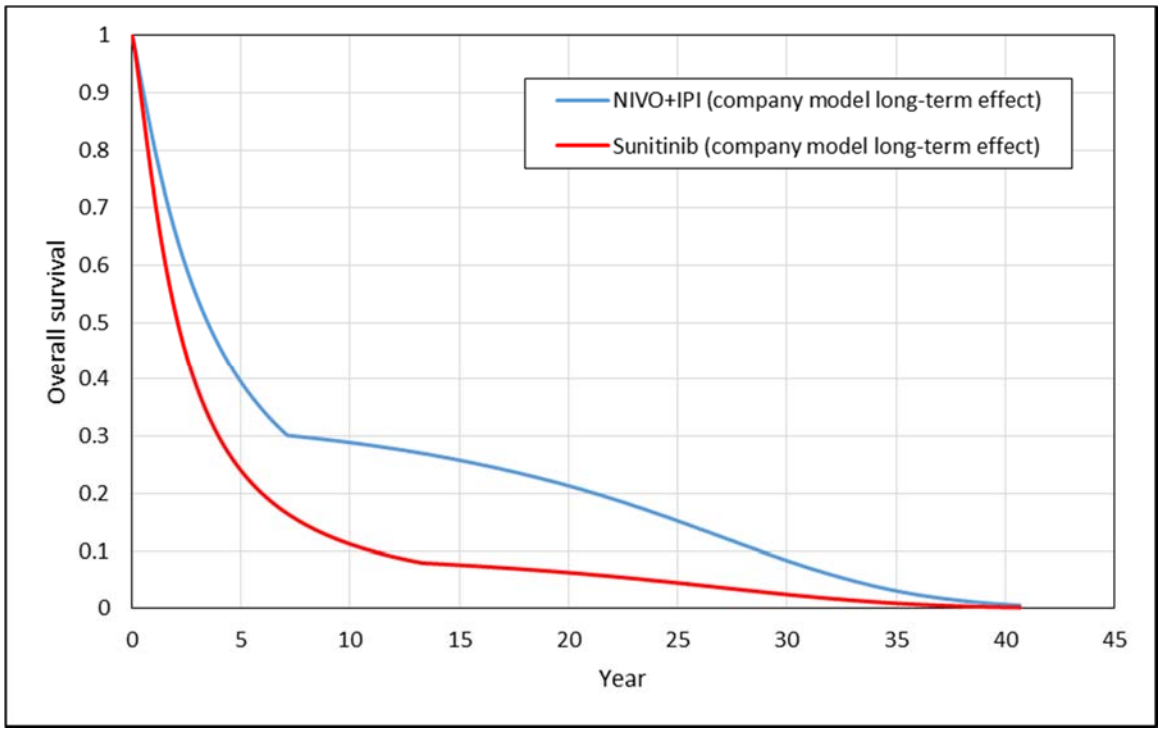

Figure 18 Company OS log-logistic curves including general mortality rate assumption (with 100% probability of immunotherapeutic effect)

Source: Company model

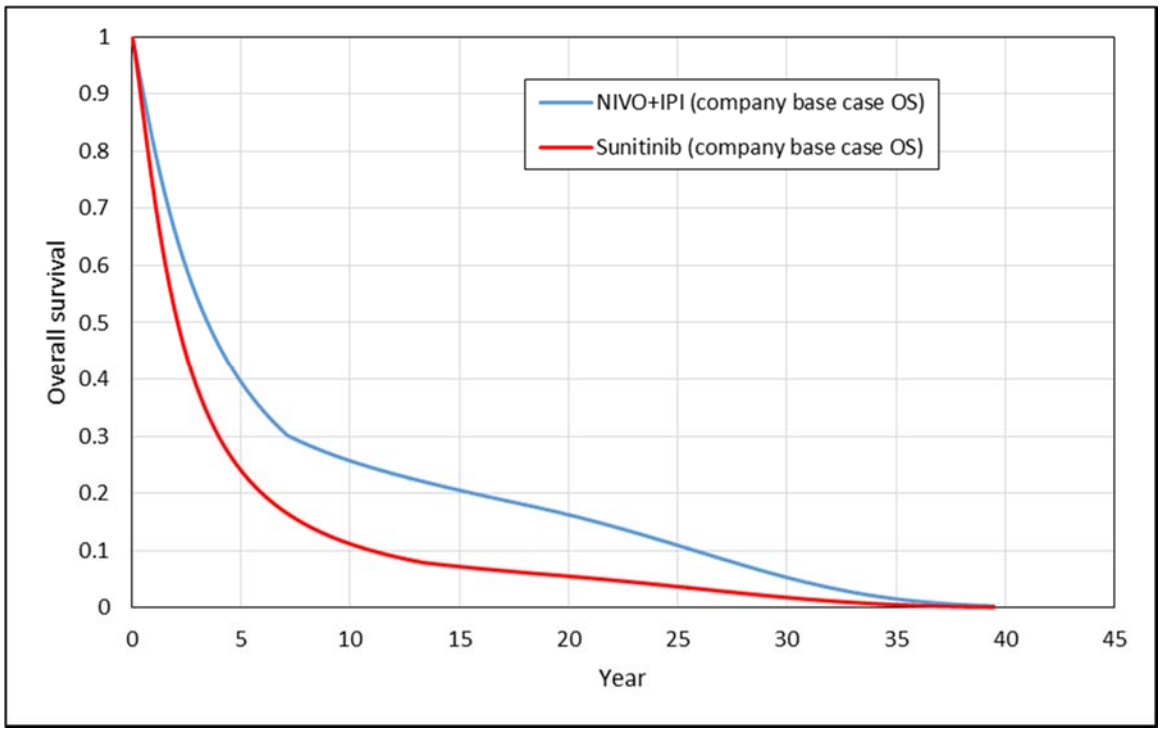

Figure 19 Company base case OS curves

Source: company model

Using a log-logistic curve to model OS without adjusting for an immunotherapeutic effect results in ever-decreasing mortality rates that drop below general population mortality rates at around 20 years after beginning treatment (Figure 20). This means that patients treated with either NIVO+IPI or sunitinib will have a lower risk of death than the general population after 20 years. The ERG notes that the company has included a cap in the model to ensure that OS mortality rates do not fall below general population mortality rates. This means that there is a strict change to general population mortality at around 20 years, which indicates that all patients who have lived at least 20 years after beginning treatment with either NIVO+IPI or sunitnib will no longer be at risk from advanced RCC and should be considered cured of the disease. The company does not acknowledge this assumption in its submission.

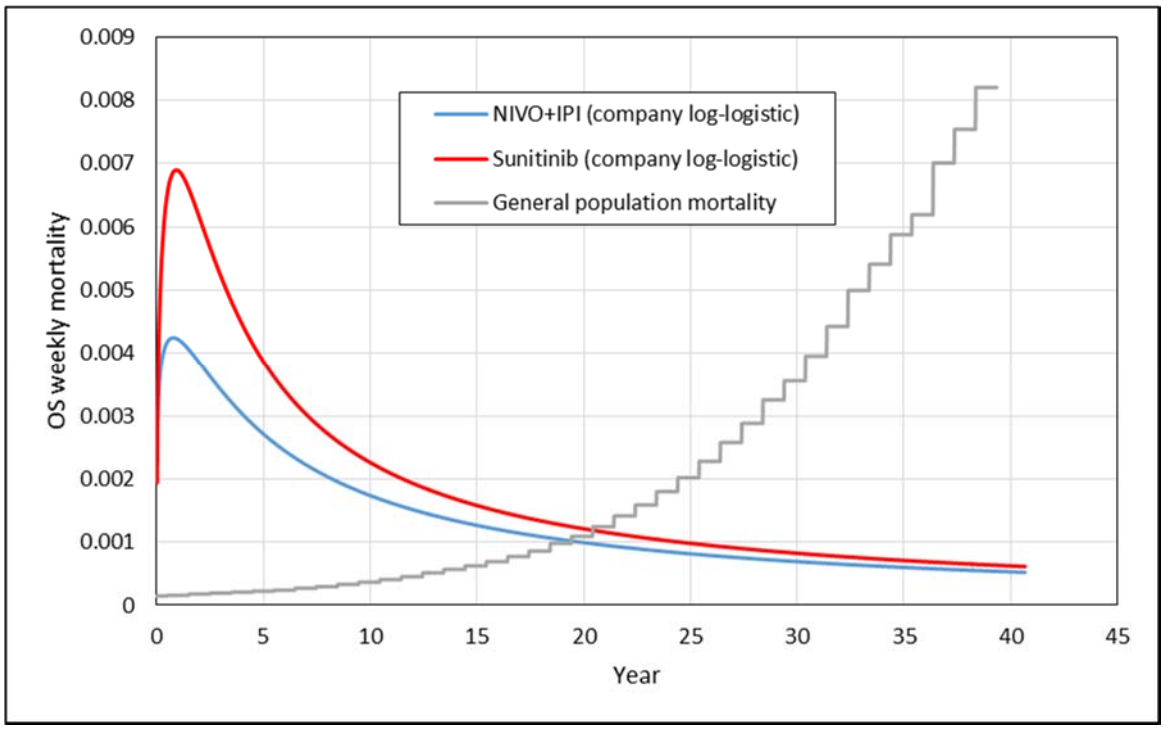

Figure 20 Weekly mortality rates in the company log-logistic model: without an immunotherapeutic effect

Source: ERG calculations based on company model

The ERG has two specific concerns regarding the company's modelling of the assumption of an immunotherapeutic effect. First, applying a strict move to general mortality when OS reaches 30% for treatment with NIVO+IPI (7.9% for treatment with sunitinib and 7.8% for treatment with pazopanib) results in a steep, clinically implausible drop in mortality rates (Figure 21). Second, applying general mortality when OS reaches a certain point does not indicate that *some* patients will be effectively cured of the disease but rather that *all* patients who live for a certain amount of time after beginning treatment will be effectively cured.

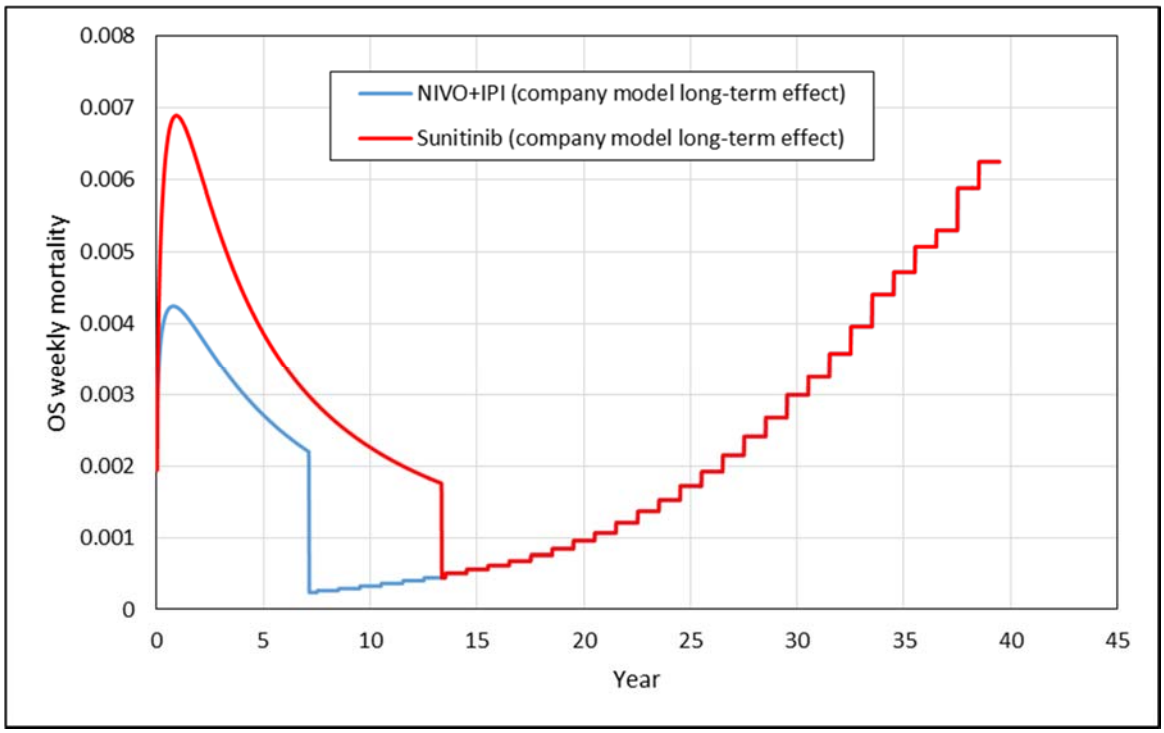

Figure 21 Weekly mortality rates in the company model: including an immunotherapeutic effect

Source: ERG calculations based on company model

Comparing the component OS curves (representing the assumption of an immunotherapeutic effect and of no immunotherapeutic effect) that make up the company's base case OS curves results in a logic problem for the base case model. The assumption of no immunotherapeutic effect for treatment with NIVO+IPI (or for treatment with nivolumab in the second-line setting) leads to mortality rates lower than general mortality after 20 years for patients treated with both NIVO+PI and with sunitinib (the company's mortality cap for the assumption of no immunotherapeutic effect does not apply in the combined base case model). The assumption of an immunotherapeutic effect leads to general mortality rates after less than 20 years. This means that not experiencing an immunotherapeutic effect is indicative of better survival prospects from 20 years after beginning treatment.

5.4.7 Progression-free survival

Clinical definition of PFS

The ERG considers that the company IRRC-assessed PFS (primary definition) in the cost effectiveness model potentially overestimates PFS gain for treatment with NIVO+IPI. As noted in Section 4.5, the ERG prefers the secondary definition of PFS used in the CheckMate 214 trial. This is because the censoring rules used in the primary definition of PFS may be an example of informative censoring, which could bias the results.

Investigation of the PFS data provided by the company during the clarification process indicates that median PFS, median PFS gain, and the overall shape of PFS, differs depending on whether the tumour assessments were made locally or centrally (*** [redacted] 22 [redacted]). The ERG is not aware of an explanation for these differences in tumour assessments that might indicate which record of PFS is more reliable. The ERG generally prefers the investigator-assessed PFS data for use in cost-effectiveness modelling, as costs associated with health state will be predicated upon the tumour assessments conducted by the clinicians treating the patients. Also, since there is some uncertainty as to which PFS assessment is more reliable, the investigator-assessed PFS represents a conservative estimate of PFS for both treatments and of PFS gain.

[redacted] 22 [redacted]

Source: Company clarification response B1

5.4.8 Time to treatment discontinuation

Treatment stopping rule for NIVO+IPI

The company base case includes the assumption that treatment with NIVO+IPI will stop at 5 years, as the company states that staying on treatment for 5 years would be a burden on the patient. Although very few patients are modelled to receive treatment with sunitinib or pazopanib beyond around 4 years, the company model still includes a small percentage of patients who would receive these drugs for longer than 5 years. The company does not explore the impact of a stopping rule for treatment with NIVO+IPI on PFS or OS outcomes. Given that the licence for nivolumab does not specify a treatment-stopping rule and the

company does not consider the impact of a stopping rule on other time-to-event outcomes , the ERG does not consider the company to be justified in assuming a stopping rule in its base case.

The ERG has investigated the impact of removing the 5-year treatment stopping rule from the company's base case using a function already included in the company model. Without the 5-year treatment stopping rule for nivolumab, the ICER per QALY gained for treatment with NIVO+IPI versus sunitinib increases by £1,589 to £29,658. Without the 5-year treatment stopping rule for nivolumab, the ICER per QALY gained for treatment with NIVO+IPI versus pazopanib increases by £1,589 to £29,611.

Model fitting: NIVO+IPI and sunitinib

The principal issue with fitting TTD curves to the CheckMate 214 data is that the data do not indicate the long-term trend expected by the company for treatment with NIVO+IPI. [redacted]. The company has investigated models that provide better visual and statistical fit to the K-M data than [redacted].

[redacted] 23 shows that the [redacted] TTD for much of the data until around [redacted] for treatment with NIVO+IPI and until around [redacted] for treatment with sunitinib. The TTD model for treatment with NIVO+IPI only really appears to fit well after around [redacted], which is the point at which heavy right-censoring may obscure the underlying trend. The result of systematically [redacted] TTD until close to the end of the available K-M data is a parametric curve that [redacted].

[redacted] 23 [redacted]

Source: company model

The ERG notes that the spline models investigated by the company improved both statistical and visual fit to the K-M data over all the standard parametric curves. The statistically best-fitting models investigated by the company are the [redacted] with NIVO+IPI and the spline hazard 1-knot for treatment with sunitinib ([redacted] 24). These two spline models both result in discontinuation rates that [redacted]. This is compared to [redacted] predicted by the company base case [redacted] ([redacted] 25).

[redacted][24]

Source: company model

[redacted][25]

The ERG assumes from interrogation of the company's spline models that the position of the knots in each of the models has been defined by default using statistical software. The position of the knots influences the long term hazard estimates, so the ERG would expect that altering the position of knots (choosing appropriate positions based on visual inspection of the data) might lead to long-term estimates more in line with clinical expectation.

Using the company's spline models [redacted] TTD from [redacted] in the company base case to [redacted] with a 5-year stopping rule and [redacted] without a stopping rule for treatment with NIVO+IPI and from [redacted] to [redacted] for treatment with sunitnib.

Using the company's spline models with a 5-year stopping rule for TTD increases the ICER per QALY gained by £2,525 to £30.593 for treatment with NIVO+IPI versus treatment with sunitinib and by £2,539 to £30,561 versus pazopanib.

Using the company's spline models without a stopping rule for TTD increases the ICER per QALY gained by £19,488 to £47,557 for treatment with NIVO+IPI versus treatment with sunitinib and by £19,509 to £47,531 versus pazopanib.

Model fitting: pazopanib

The ERG does not consider the company to be justified in adjusting the TTD curve for treatment with pazopanib to be greater than TTD for treatment with sunitinib. The company has estimated TTD for treatment with pazopanib by applying an HR to the modelled TTD curve for treatment with sunitinib, which the company has estimated as the ratio of median TTD for each treatment in the COMPARZ trial. The ratio of median TTD in the COMPARZ trial was 0.95 for treatment with sunitinib versus treatment with pazopanib.

First, [redacted]. Second, the reference given by the company for the median TTD for treatment with sunitinib versus treatment with pazopanib[106] does not include confidence intervals for these estimates. Given that PFS is not shown to be significantly different for treatment with sunitinib versus treatment with pazopanib in the COMPARZ trial (Section 4.7.7, Table 15) and patients were predominantly treated to progression, the ERG does not consider it justified to assume that TTD is significantly different in the two arms.

5.4.9 Utility values

The ERG considers the company's analysis of the EQ-5D-3L data from the CheckMate 214 trial to be incomplete.

The company carried out a regression-based analysis to derive mean utility values using responses to the EQ-5D-3L questionnaire from the CheckMate 214 trial. The company used a stepwise procedure to consider the impact of three main effects (treatment arm, treatment status and progression status) on utility value. The company's final utility model used to estimate utility values in the first-line setting includes treatment arm and treatment status, plus an interaction term.

The company considered seven utility models as part of the stepwise procedure, which represent combinations of all three main effects except one: treatment arm and progression status. However, there are only eight possible models using the three main effects chosen by the company. The ERG would have preferred the company to have presented models for all eight combinations of the main effects to allow for a full consideration of the most appropriate utility model.

The ERG notes that the company has presented the utility values used in TA417[115] for comparison (CS, Table 29) and states that these values provide evidence of consistency across similar trials. However, during TA417, the company's base case utility model included only the effects of treatment and progression status. Given that the company in the current appraisal has not provided estimates for a utility model that includes only the effects of treatment and progression status, it is not possible to directly compare the utility values used in this appraisal with those in TA417.

5.4.10 Subsequent treatments

In general, the ERG prefers estimates of the proportion of patents who receive subsequent treatments to be linked directly to the source of OS, PFS and TTD outcomes. This is because OS and PFS outcomes will be linked to the treatments the patients actually received, rather than those they might receive in UK clinical practice. Estimates of TTD might also be linked to the potential second-line treatments available to patients, as the clinical decision to discontinue treatment may be based partly on the available choice of subsequent therapies.

The ERG has investigated the impact on the ICERs per QALY gained of assuming that subsequent treatments are received in the same proportions as in the CheckMate 214 trial. Assuming subsequent treatments are received in the same proportions as in the CheckMate 214 trial reduces the company's base case ICER per QALY gained by £1,582 to £26,486 for treatment with NIVO+IPI versus treatment with sunitinib and by £1,565 to £26,457 for treatment with NIVO+IPI versus treatment with pazopanib.

Since the company's base case assumption results in a higher ICER per QALY gained than using the proportions of subsequent treatments from the CheckMate 214 trial and given the uncertainty surrounding which subsequent treatments might be used in clinical practice if treatment with NIVO+IPI were to be recommended for intermediate/poor risk patients with advanced RCC, the ERG considers the company's base case assumption to be conservative. However, it should be noted that OS, PFS and TTD may differ in clinical practice compared with the CheckMate 214 trial if the proportion of subsequent treatments are inconsistent.

5.4.11 Treatment administration costs

The company has not included a cost for administering treatment with sunitinib or treatment with pazopanib. The ERG does not consider this to reflect the costs incurred in clinical practice.

5.5 ERG exploratory analysis

5.5.1 Risk groups

Results of the ERG's analysis suggest that the response to treatment may be different in the two risk groups, which may affect long-term trends that are not currently obvious from analysis of the K-M data for the combined intermediate/poor risk group (see Section 5.4.4 of this ERG report). However, the ERG does not consider it justifiable to model time-to-event outcomes separately for the two risk groups in this current appraisal given the immaturity of the OS data from the CheckMate 214 trial.

Analysis of OS data by risk group (Section 5.4.4) shows that the OS events recorded in the CheckMate 214 trial by the time of the data cut [redacted]42[redacted]42[redacted]42[redacted]42[redacted]42. Given that the intermediate-risk group is larger than the poor-risk group in the CheckMate 214 trial, this means that the mortality risk associated with the intermediate-risk group is likely to come to dominate the mortality risk for the combined intermediate/poor risk group over time as fewer poor-risk patients are left at risk. This means that long-term trends in the combined intermediate/poor risk group will likely begin to more closely reflect trends in the intermediate risk group. However, the ERG cautions that the OS data are too immature for the intermediate-risk group to be able to estimate with any certainty what those long-term trends might be.

5.5.2 Overall survival

Assumption of immunotherapeutic effect

In the absence of conclusive long-term evidence regarding the existence and/or form of a long-term survival effect linked to first-line treatment with NIVO+IPI (and nivolumab monotherapy in the second-line setting) for patients with advanced RCC (Section 5.4.3 of this ERG report), the ERG does not consider it justifiable to assume such an effect in the base case.

Using only the company's modelling of the assumption of 'no immunotherapeutic effect on OS' results in an increase in the ICER per QALY gained of £5,323 to £33,392 for treatment with NIVO+IPI versus sunitinib and of £5,359 to £33,381 for treatment with NIVO+IPI versus pazopanib.

Alternative methods of modelling OS

The ERG has explored alternative methods of modelling OS in order to resolve the issues connected to the use of a log-logistic curve (Section 5.4.6).

Appraisal of the cumulative hazard plot for OS from the CheckMate 214 trial indicates that there exists a constant hazard trend from around 7 months, as represented by a straight line (Figure 26), which indicates an exponential trend.

The ERG acknowledges that heavy right-censoring after the minimum follow-up of 17.5 months may influence the shape of the curve and that a long-term trend may not in reality be established until later. Given that the evidence from other trials of nivolumab, ipilimumab and sunitinib indicates a pattern of decreasing hazards in the first 3 to 5 years after beginning treatment (Section 5.4.3), appending an exponential tail to the OS data from the CheckMate 214 trial data represents a conservative estimate of long-term survival for both treatments.

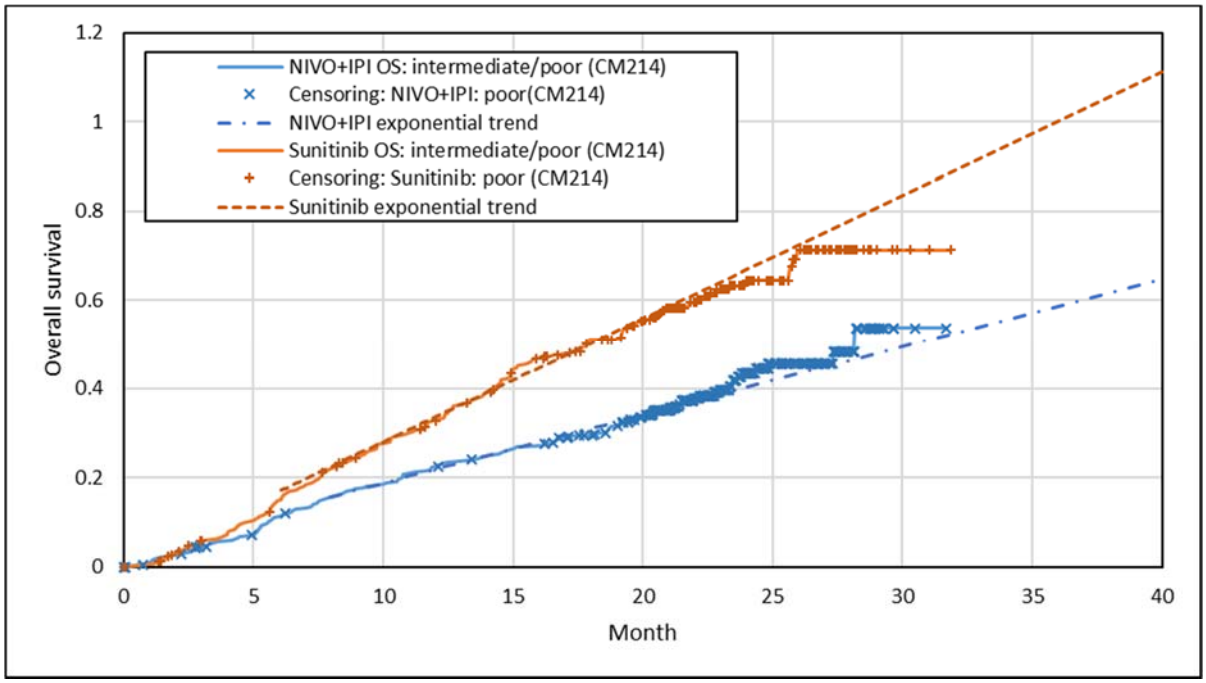

Figure 26 Cumulative hazard plot of OS (CheckMate 214)

Source: Company clarification response question B1

The ERG has remodelled OS for treatment with NIVO+IPI and for treatment with sunitinib by appending independent exponential curves to the K-M data at 22 months for each treatment. Use of an exponential tail does not preclude a proportion of patients within this tail from being cured or achieving long-term survival without full cure.

Figure 27 shows OS in the company base case and in the ERG's remodelled exploratory analysis with no immunotherapeutic effect for treatment with NIVO+IPI and for treatment with sunitinib. Table 32 compares OS outcomes for the company base case versus the ERG's exploratory analysis of no immunotherapeutic effect.

Table 32 Mean life years gained and OS at 5 years, 10 years and 15 years in company model and ERG exploratory analysis

	OS: 5 years		OS: 10 years		OS: 15 years		Mean life years		
	NIVO+ IPI	Sun	NIVO+ IPI	Sun	NIVO+ IPI	Sun	NIVO+ IPI	Sun	Gain
Company	39.5%	24.0%	25.7%	11.2%	20.6%	7.2%	8.04	4.53	3.51
ERG	38.5%	19.2%	15.3%	3.6%	6.1%	0.7%	5.26	2.03	3.23
Difference	*-1.0%*	*-4.8%*	*-10.4%*	*-7.6%*	*-14.5%*	*-6.5%*	*-2.78*	*-2.50*	*-0.28*

OS=overall survival; Sun=sunitinib
Source: company model; ERG calculations

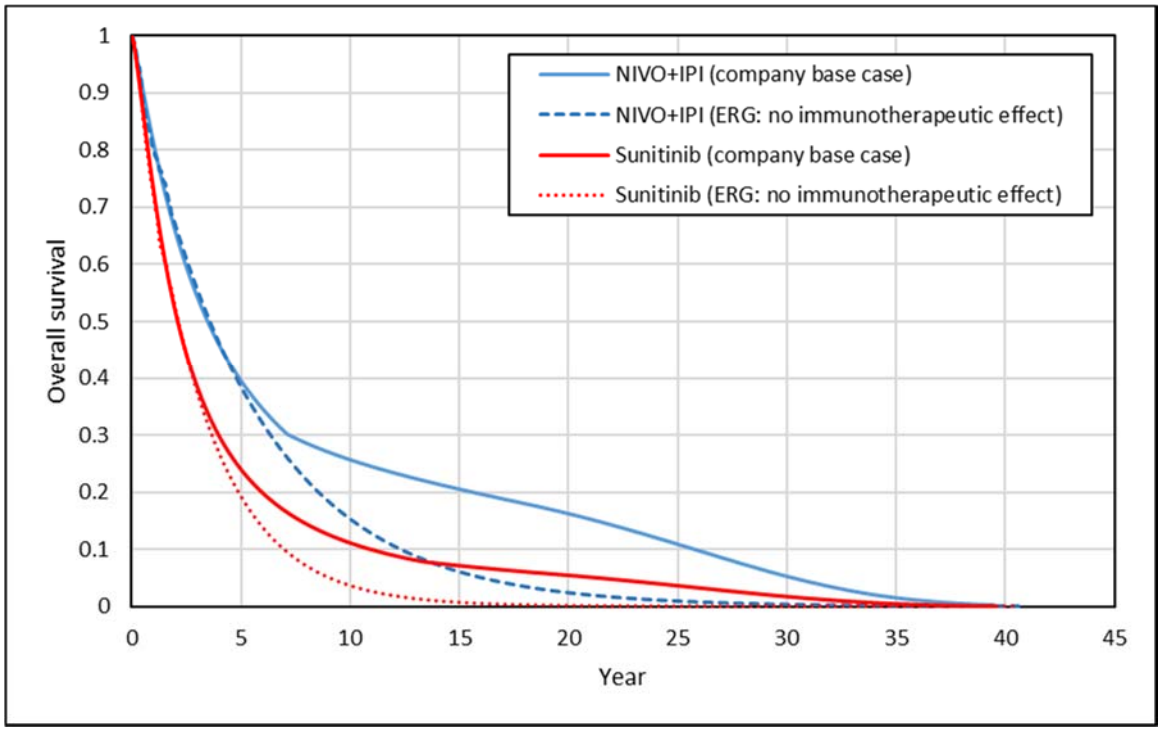

Figure 27 ERG OS and company base case OS

Source: Company model; ERG

Using the ERG's remodelled OS results in an increase of [redacted] in the ICER per QALY gained to [redacted] for treatment with NIVO+IPI versus sunitinib and an increase of [redacted] to [redacted] for treatment with NIVO+IPI versus pazopanib.

5.5.3 Progression-free survival

The ERG has investigated the impact of remodelling PFS from the CheckMate 214 trial using the investigator-assessed, secondary definition of PFS. The ERG prefers the secondary definition in principle, as it does not contain the same potential for bias due to informative censoring as the primary definition of PFS although it acknowledges that the use of the primary definition led to similar results in this instance (see Section 4.6.2 of this ERG report). The ERG

prefers the use of investigator-assessed PFS in cost-effectiveness modelling, as it is more representative of the treatment patients will receive related to their health state.

Examination of the cumulative hazard plot ([redacted]28[redacted]) indicates exponential trends from around 8 months to the end of the K-M data in both arms. The ERG has therefore fitted a piecewise model using the K-M data as far as possible (until 22 months for treatment with NIVO+IPI and until 21 months for treatment with sunitinib) to accurately capture the features of the trial data before appending exponential tails (Figure 29). The parameters for the exponential tails have been calculated using data from 8 months onwards for both treatments.

[redacted]28[redacted]

Source: Company clarification response question B1

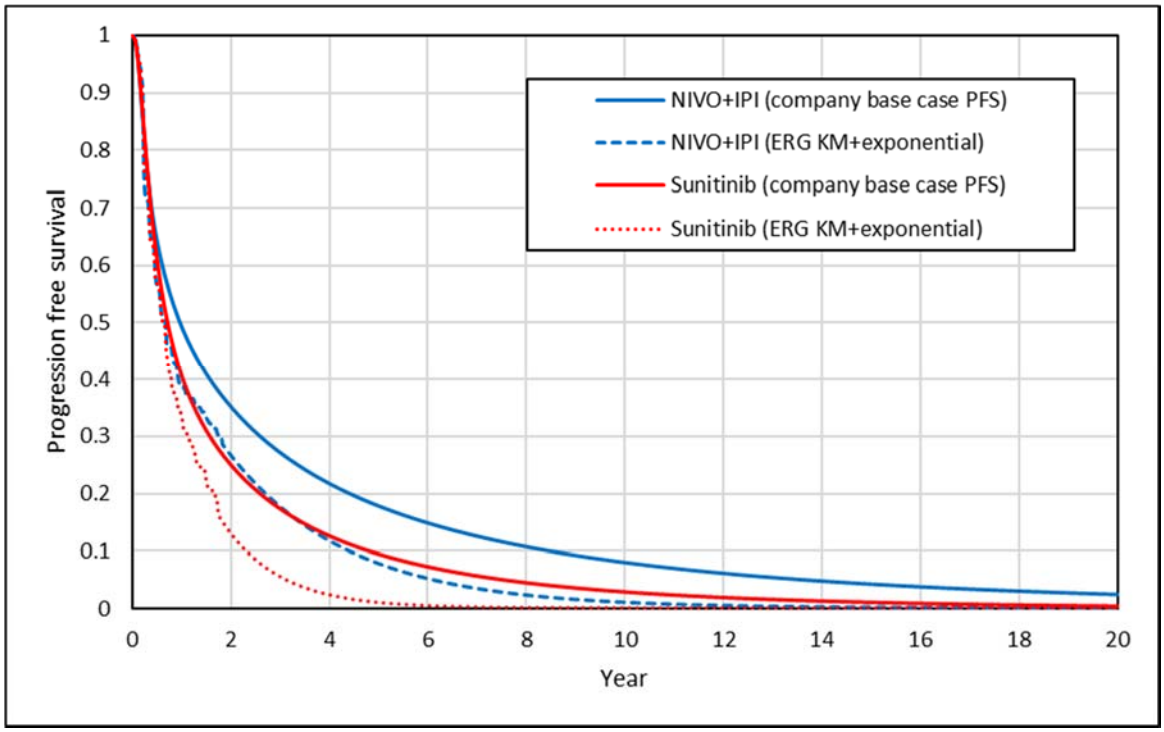

Figure 29 ERG PFS and company base case PFS

Source: ERG calculations; company model

Appending an exponential curve to the (investigator-assessed, secondary definition) PFS K-M data decreases mean PFS from 23.8 months to 14.2 months for treatment with NIVO+IPI and from 14.8 months to 8.6 months for treatment with sunitinib. Mean PFS gain is reduced from 9.0 months to 5.5 months. Using the ERG's PFS model increases the ICER per QALY gained by £859 to £28,928 for treatment with sunitinib and by £871 to £28,892 for treatment with pazopanib.

5.5.4 Time to treatment discontinuation

Model fitting: NIVO+IPI

The ERG has explored the viability of extrapolating TTD for treatment with NIVO+IPI that [redacted]. Appending a parametric curve to the existing K-M data allows the early features of the data to be captured accurately whilst [redacted]. Examination of the cumulative hazard plots ([redacted] 30) suggests an exponential trend in the data for treatment with NIVO+IPI from around [redacted] and for treatment with sunitinib from around [redacted]. The final two data points on the plot for treatment with sunitinib represent discontinuation events when only 3 and 2 patients were left at risk, so the effect of these events on the K-M estimates is exaggerated. The ERG has appended exponential curves to the K-M data for both treatments at 22 months ([redacted] 31).

The exponential curves are parameterised using the K-M data from 10 months in the NIVO+IPI arm and 14 months in the sunitnib arm.

[redacted]30

Source: Company clarification response B1

[redacted]31

Source: Company clarification response B1; ERG

Comparison of the ERG's revised TTD models with the company's [redacted] models (without stopping rule) shows similar long-term trends in the two approaches ([redacted]32). Using exponential curves appended to the K-M data increases TTD from [redacted] in the company base case ([redacted] without a stopping rule) to [redacted] without a stopping rule for treatment with NIVO+IPI and from [redacted] to [redacted] for treatment with sunitnib.

[redacted]32 [redacted]

Source: company model; ERG calculations

Using the ERG's revised TTD models (without stopping rule for treatment with NIVO+IPI) increases the ICER per QALY gained by £4,051 to £32,119 for the comparison of treatment with NIVO+IPI versus treatment with sunitnib and by £4,099 to £32,121 for the comparison of treatment with NIVO+IPI versus treatment with pazopanib.

Model fitting: pazopanib

The ERG has investigated the effect of assuming that TTD for treatment with pazopanib is equal to TTD for treatment with sunitinib.

Assuming that TTD is equal for treatment with sunitinib and treatment with pazopanib increases the ICER per QALY gained for treatment with NIVO+IPI versus treatment with pazopanib by £184 to £28,206.

5.5.5 Utility values

The ERG has investigated the models presented by the company in Table 28 of the CS to assess the probability that any of the alternative models presented by the company would provide a better fit to the data than the utility model used in the company base case. Comparing the AIC statistics for each of the models presented by the company indicates that there is substantial comparative evidence for the company's Model 7, which includes all three main effects plus interaction terms; all other models have limited comparative evidence to support them. The method for assessing the evidence for each of the utility models using Akaike weights is described by Wagenmakers and Farrell.[116]

The ERG has calculated mean utility values using Model 7 to investigate the effect of using alternative utility values in the cost effectiveness model. Introducing the effect of progression status in Model 7 produces utility estimates for the PPS (on treatment) state that are higher than any other state in the model (Table 33). This result may be explained with reference to the type of patients expected to move into the PPS (on treatment) health state and who contribute to the calculation of the utility value for that state. Patients in the CheckMate 214 trial were permitted to continue to receive treatment beyond progression if their clinician considered them to be deriving clinical benefit and tolerating the drug. It is therefore plausible that only patients who were doing well and not experiencing AEs, and who could be considered fitter and more likely to be experiencing a good HRQoL, would enter into the PPS (on treatment) state.

Table 33 Alternative utility values from CheckMate 214

State	Model 5: treatment status and treatment arm		Model 7: treatment status, treatment arm and progression status	
	NIVO+IPI	Sunitinib	NIVO+IPI	Sunitinib
PFS (on treatment)	0.793	0.751	0.793	0.750
PFS (off treatment)	0.719	0.699	0.737	0.703
PPS (on treatment)	0.793	0.751	*0.794*	*0.763*
PPS (off treatment)	0.719	0.699	0.701	0.694

PFS=progression free survival; PPS=post-progression survival
Source: CS, Table 33; ERG calculations based on CS, Table 28

The PPS (on treatment) utility value has no effect on the outcome of the model, as no patients are modelled to enter this state. This is because (IRRC-assessed) PFS is greater than TTD at all times in the CheckMate 214 trial.

Applying the utility values calculated using the company's Model 7, including all three main effects, increases the base case ICER per QALY gained for treatment with NIVO+IPI by £434

to £28,503 versus treatment with sunitinib and by £430 to £28,452 versus treatment with pazopanib.

5.5.6 Treatment administration costs

The ERG has investigated the impact of including administration costs for treatment with sunintib and treatment with pazopanib. Applying a unit cost of £164 per cycle (SB11Z Deliver exclusively oral chemotherapy [outpatient]117) reduces the ICER per QALY gained by £2,740 to £25,328 for treatment with NIVO+IPI versus treatment with sunitinib and by £4,222 to £23,800 for treatment with NIVO+IPI versus treatment with pazopanib.

5.6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has carried out the following revisions to the company base case ICERs for treatment with NIVO+IPI versus treatment with sunitinib and versus treatment with pazopanib:

- Removal of the immunotherapeutic survival effect from company model [R1]
- ERG remodelled OS estimates from CheckMate 214 [R2]
- ERG remodelled PFS estimates from CheckMate 214 [R3]
- Removal of the TTD stopping rule from company model [R4]
- ERG remodelled TTD estimates from CheckMate 214 (without stopping rule) [R5]
- Assumed pazopanib TTD=sunitinib TTD [R6]
- Model 7 utility values including all three main effects [R7]
- Subsequent treatments in the proportions received in CheckMate 214 [R8]
- Addition of treatment administration costs for sunintinib and pazopanib [R9]

Details of all Microsoft Excel revisions carried out by the ERG to the company's model are presented in Appendix 6 of this ERG report (Section 9.6).

A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results (using PAS prices for first-line treatments) for the comparison of treatment with NIVO+IPI and treatment with sunitinib are shown in Table 34. A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results (using PAS prices for first-line treatments) for the comparison of treatment with NIVO+IPI and treatment with pazopanib are shown in Table 35.

The ERG's revised base case includes the ERG's remodelled PFS, OS and TTD estimates; the assumption that outcomes for treatment with pazopanib are the same as for treatment with sunitinib; utility values calculated using treatment arm, treatment status and progression status; subsequent treatment from the CheckMate 214 trial; and administration costs for treatment with sunitinib and pazopanib. The ERG's revised base case does not include an assumption of an additional immunotherapeutic survival effect or a treatment stopping rule for treatment with NIVO+IPI.

Table 34 Cost effectiveness using PAS prices (NIVO+IPI versus sunitinib): ERG revisions to company base case

Revision	NIVO+IPI			Sunitinib			Incremental			ICER per QALY gained	Change from corrected base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company original base case	[redacted]	***4.43***	***8.04***	[redacted]	***2.68***	***4.53***	***£50,500***	***1.75***	***3.51***	***£28,865***	
Company corrected base case	[redacted]	***4.43***	***8.04***	[redacted]	***2.68***	***4.53***	***£49,106***	***1.75***	***3.51***	***£28,068***	
R1) Remove IO effect from company model	[redacted]	4.07	7.11	[redacted]	2.65	4.43	£47,521	1.42	2.68	£33,392	+£5,323
R2) ERG OS (without IO)	[redacted]	3.34	5.26	[redacted]	2.03	3.03	£47,320	1.30	2.22	£36,327	+£8,259
R3) ERG PFS	[redacted]	4.43	8.04	[redacted]	2.70	4.53	£50,131	1.73	3.51	£28,928	+£859
R4) Remove TTD stopping rule	[redacted]	4.43	8.04	[redacted]	2.68	4.53	£52,024	1.75	3.51	£29,658	+£1,589
R5) ERG TTD (without stopping rule)	[redacted]	4.44	8.04	[redacted]	2.68	4.53	£56,593	1.76	3.51	£32,119	+£4,051
R6) Assume pazopanib TTD =sunitinib TTD	[redacted]	-	-	[redacted]	-	-	-	-	-	-	-
R7) Model 7 utilities	[redacted]	4.39	8.04	[redacted]	2.67	4.53	£49,106	1.72	3.51	£28,503	+£434
R8) Subsequent treatment proportions match CheckMate 214	[redacted]	4.43	8.04	[redacted]	2.64	4.44	£47,343	1.79	3.60	£26,486	-£1,582
R9) Add administration costs for sunitinib and pazopanib	[redacted]	4.43	8.04	[redacted]	2.68	4.53	£44,312	1.75	3.51	£25,328	-£2,740
ERG revised base case (R2, R3, R5, R7, R8, R9)	[redacted]	***3.31***	***5.26***	[redacted]	***2.04***	***3.03***	***£48,331***	***1.27***	***2.22***	***£38,152***	***+£10,083***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; IMAE=immune-mediated adverse events; IO=immunotherapeutic effect; LY=life years; OS=overall survival; PFS=progression free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 35 Cost effectiveness using PAS prices (NIVO+IPI versus pazopanib): ERG revisions to company base case

Revision	NIVO+IPI			Pazopanib			Incremental			ICER per QALY gained	Change from corrected base case
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company original base case	[redacted]	***4.43***	***8.04***	[redacted]	***2.68***	***4.52***	***£50,423***	***1.75***	***3.51***	***£28,819***	
Company corrected base case	[redacted]	***4.43***	***8.04***	[redacted]	***2.68***	***4.52***	***£49,029***	***1.75***	***3.51***	***£28,022***	
R1) Remove IO effect from company model	[redacted]	4.07	7.11	[redacted]	2.65	4.43	£47,433	1.42	2.68	£33,381	+£5,359
R2) ERG OS (without IO)	[redacted]	3.34	5.26	[redacted]	2.04	3.03	£47,259	1.30	2.22	£36,341	+£8,319
R3) ERG PFS	[redacted]	4.43	8.04	[redacted]	2.70	4.52	£50,074	1.73	3.51	£28,892	+£871
R4) Remove TTD stopping rule	[redacted]	4.43	8.04	[redacted]	2.68	4.52	£51,947	1.75	3.51	£29,611	+£1,589
R5) ERG TTD (without stopping rule)	[redacted]	4.44	8.04	[redacted]	2.68	4.52	£56,587	1.76	3.51	£32,121	+£4,099
R6) Assume pazopanib TTD=sunitinib TTD	[redacted]	4.43	8.04	[redacted]	2.67	4.52	£49,414	1.75	3.51	£28,206	+£184
R7) Model 7 utilities	[redacted]	4.39	8.04	[redacted]	2.67	4.52	£49,029	1.72	3.51	£28,452	+£430
R8) Subsequent treatment proportions match CheckMate 214	[redacted]	4.43	8.04	[redacted]	2.64	4.44	£47,238	1.79	3.60	£26,457	-£1,565
R9) Add administration costs for sunitinib and pazopanib	[redacted]	4.43	8.04	[redacted]	2.68	4.52	£41,642	1.75	3.51	£23,800	-£4,222
ERG revised base case (R2, R3, R5, R6, R7, R8, R9)	[redacted]	***3.31***	***5.26***	[redacted]	***2.04***	***3.03***	***£46,540***	***1.27***	***2.22***	***£36,738***	***+£8,716***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; IMAE=immune-mediated adverse events; IO=immunotherapeutic effect; LY=life years; OS=overall survival; PFS=progression free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

5.7 Conclusions of the cost effectiveness section

The ERG's revised base case yields an ICER of £38,152 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with sunitinib, which is £10,083 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are lower -£775) than those generated by the company for this comparison and incremental benefits that are lower (-0.49 QALYs) than those generated by the company.

The ERG's revised base case yields an ICER of £36,738 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with pazopanib, which is £8,716 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are lower -£2,490) than those generated by the company for this comparison and incremental benefits that are lower (-0.49 QALYs) than those generated by the company.

For both comparisons, the differences between the ERG revised base case and the company's corrected base case are principally a result of the ERG's modelling of OS, which decreases incremental life years and QALYs substantially but also decreases incremental costs, and the ERG's modelling of TTD, which increases incremental costs.

The ERG's remodelling of PFS and TTD result in very little difference between the two outcomes. Given that IRRC-assessed and investigator-assessed PFS differ substantially, and that treatment discontinuation decisions will be taken by the investigator alongside the patient, it is not surprising that using investigator-assessed data results in modelled PFS that is closer to TTD than using IRRC-assessed PFS.

There remains considerable uncertainty in the modelling of OS, since the data from the CheckMate 214 trial are immature and subject to heavy right censoring. In total, OS is censored for 67% of patients in the NIVO+IPI arm of the CheckMate 214 trial, the vast majority of which (94%) is censored after minimum follow-up of 17.5 months. For the sunitinib arm of the CheckMate 214 trial, OS is censored for 55% of patients in total, 86% of which occurs after 17.5 months. This means that long-term survival trends may not yet have been established or may be obscured by the weight of censoring in the final few months of data. There is also uncertainty about the relative contribution to OS from the intermediate and poor risk groups separately, which may impact the long-term survival trends for the combined group.

Uncertainty also remains around the existence and/or form of any immunotherapeutic effect on survival. The lack of long-term data on treatment with nivolumab and/or ipilimumab for advanced RCC means that it is not yet possible to conclude from the evidence whether or not such an effect exists and, if so, who might benefit from it and to what extent.

6 END-OF-LIFE CRITERIA

The NICE End-of-Life criteria, and the data presented by the company in relation to End-of-life treatment considerations are summarised in Table 36.

Table 36 End-of-Life criteria

NICE End-of-Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company states (CS, p63) that: • clinical evidence (Phase III RCT data and real-world evidence) indicates that around half of intermediate/poor risk patients are unlikely to survive for more than 2 years when treated with VEGFR-TKI agents in the first-line setting • life expectancy can be as low as 6 months for poor risk patients These considerations are also summarised in Table 19 of the CS
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	The company states (CS, p63) that: • the economic model based on CheckMate 214 trial data has shown a survival gain in the order of years, rather than months These considerations are also summarised in Table 19 of the CS

6.1 Short life expectancy

The ERG has summarised median OS of treatment with VEGFR-TKIs, using the same six studies (two RCTs [CheckMate 214 and the COMPARZ trials] and four real-world studies used by the company) in Table 37. Based on median OS, the ERG considers the published evidence shows poor risk patients meet the NICE End-of-Life criterion of life-expectancy <24 months (all six studies report median OS <11 months for this subgroup). However, it is uncertain from the evidence presented whether intermediate risk patients meet this criterion (from five studies, median OS varied from 14.6 to 28.5 months with the median [redacted] in the CheckMate 214 trial).

The CheckMate 214 trial is the only source of OS evidence for the combined intermediate/poor risk population. The evidence does not support life-expectancy <24 months whether considering median OS ([redacted]) or mean OS ([redacted]).

It is important to note, however, that there were 3.7 times as many patients with intermediate risk status than poor risk status in the CheckMate 214 trial. The ratio of intermediate risk to poor risk patients seen in clinical practice may be smaller (based on clinical opinion received by the ERG, see Section 4.3.2, and on data from two large population studies, see Table 38). If so, the CheckMate 214 trial may be overestimating life expectancy for the intermediate/poor risk group as a whole given the differences in expected life expectancy reported for the subgroups individually (as summarised in Table 37).

Table 37 Overall survival reported for patients treated with VEGFR-TKIs in studies of advanced RCC

Study	Median OS (months)	
	Intermediate risk	Poor risk
International, population-based study validating IMDC (Heng et al 2013)[72 72]	Sunitinib 22.5	Sunitinib 7.8
Population-based study (Czech Republic),[118] modified MKSCC and IMDC assessed risk (Kubackcova et al 2015)[a]	Sunitinib (i) 28.5 Sunitinib (ii) 24.8	Sunitinib (i) 10.6 Sunitinib (ii) 9.3
Population-based study (Netherlands),[119] modified MKSCC assessed risk (de Groot et al 2016)[b]	Sunitinib (i) 14.6 Sunitinib (ii) 16.6	Sunitinib (i) 6.1 Sunitinib (ii) 6.5
Global expanded access programme of sunitinib (Gore et al 2015), IMDC assessed[c]	Sunitinib 18.9	Sunitinib 6.2
CheckMate 214 trial, IMDC assessed risk[d]	[redacted]	[redacted]
COMPARZ trial, MKSCC assessed risk	Sunitinib 26.1 Pazopanib 26.9	Sunitinib 7.7 Pazopanib 9.9

IMDC= The International Metastatic Renal Cell Carcinoma Database Consortium; MKSCC=Memorial Sloan Kettering Cancer Center; NR=not reached; OS-overall survival
a Only data reported using the IMDC model are reported by the company, data reported here are reported using (i) MKSCC and (ii) IMDC model. The ERG notes that Using the IMDC model, 54.1% of MSKCC poor risk patients were reclassified as intermediate risk and 20.2% of MSKCC intermediate-risk patients were reclassified as favourable risk
b Only data for the poor risk group are reported by the company; data reported here are taken from the published paper (Table 4) and are the median OS from (i) 2008 to 2010 cohort and (ii) 2011 to 2013 cohort. Data for intermediate risk group for (b) include some patients with favourable risk prognosis
c The company only report a median OS of 19.0 months from this study
d Data are immature and from post-hoc analyses requested by the ERG and should be treated with caution. Lower confidence interval in the intermediate risk group is 25.8 months
Source: adapted from CS, Table 19

Table 38 The number and proportions of patients by risk status reported in studies of advanced RCC

Risk status	Population based studies				RCTs	
	Heng et al 2013	Gore et al 2015	Kubackova et al 2015		COMPARZ trial	CheckMate 214
Model for assessing risk	IMDC	IMDC	Modified MKSCC	IMDC	MKSCC	IMDC
Patients with known risk status, n	849	4065	495	495	1072	1096
Favourable risk, n (%)	157 (18)	988 (24)	60 (12)	109 (22)	303 (28)	249 (23)
Intermediate risk, n (%)	440 (52)	2188 (54)	302 (61)	309 (62)	650 (61)	667 (61)
Poor risk, n (%)	252 (30)	889 (22)	133 (27)	77 (16)	119 (11)	180 (16)
Ratio of intermediate to poor risk	1.7	2.5	2.3	4.0	5.5	3.7

IMDC= The International Metastatic Renal Cell Carcinoma Database Consortium; MKSCC=Memorial Sloan Kettering Cancer Center; RCT=randomised controlled trial

6.2 Extension to life

The estimated mean extension to life based on economic modelling by the company is reported to be 3.51 years (42.1 months) in Table 44 of the CS. The estimated mean extension to life based on economic modelling by the ERG is 26.6 months. Therefore the ERG concurs that the gain in OS for intermediate/poor risk patients exceeds 3 months.

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

Evidence for NIVO+IPI versus an appropriate comparator (sunitinib) has been presented from the CheckMate 214 trial for patients with intermediate/poor risk advanced RCC. No direct evidence is available comparing NIVO+IPI versus the other comparator of interest (pazopanib); indirect efficacy evidence has therefore been presented for this comparison.

Overall, the evidence derived from the direct and indirect evidence suggests that NIVO+IPI is superior to both sunitinib and pazopanib in terms of OS for patients with intermediate/poor risk advanced RCC. However, given the immaturity of the OS data, it is unknown whether the OS benefit observed at the first-interim analysis of OS will be observed in the longer-term.

The ERG notes that subsequent therapy received following disease progression may impact on OS. There is uncertainty to what extent the treatments received in the CheckMate 214 trial impacted upon OS. Furthermore, subsequent treatment received in both arms of the trial differed to what clinicians would expect patients to receive in clinical practice. There is therefore also uncertainty as to how similar OS reported in the trial would be to OS observed in clinical practice.

The direct and indirect evidence appears to be generalisable to patients who would be treated in NHS practice with the following important caveats: patients in the trials tended to be younger than seen in clinical practice, had clear-cell disease and the proportion of patients who had prior nephrectomy may be greater than is now seen in clinical practice. It is therefore unclear if NIVO+IPI is preferable to VEGFR-TKIs for older patients, patients with non-clear cell RCC and patients who have not had prior nephrectomy.

There were also slightly more intermediate risk patients and slightly fewer poor risk patients in the CheckMate 214 and COMPARZ trials than would be seen in clinical practice. When taking into consideration NICE's End-of-Life criteria, this difference may be important since life expectancy differs between patients with intermediate and poor risk disease.

7.2 Cost effectiveness

The ERG's revised base case yields an ICER of £38,152 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with sunitinib, which is £10,083 higher than the company's corrected base case. The ERG's revised base case yields an ICER of £36,738 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with pazopanib, which is £8,716 higher than the company's corrected base case.

There remains considerable uncertainty in the modelling of OS, since the data from the CheckMate 214 trial are immature and subject to heavy right censoring. This means that long-term survival trends may not yet have been established or may be obscured by the weight of censoring in the final few months of data. There is also uncertainty about the relative contribution to OS from the intermediate and poor risk groups separately, which may impact the long-term survival trends for the combined group.

Uncertainty also remains around the existence and/or form of any immunotherapeutic effect on survival. The lack of long-term data on treatment with nivolumab and/or ipilimumab for advanced RCC means that it is not yet possible to conclude from the evidence whether or not such an effect exists and, if so, who might benefit from it and to what extent.

7.3 Implications for research

Further research to identify patients most at risk of developing serious autoimmune toxicity from treatment with NIVO+IPI would be of benefit to clinicians and patients.

Further research to identify predictive markers of response from treatment with NIVO+IPI would be of benefit to clinicians and patients.

Further evidence is required for the immunotherapeutic effect of nivolumab and NIVO+IPI in patients with advanced RCC.

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9 APPENDICES

9.1 Appendix 1: RECIST, immune-related response and iRECIST criteria

Hodi et al 2016[91] presented a comparison of the requirements that define a response using the RECIST and immune-related response criteria. Their comparison is reproduced in Table 39. A comparison of the RECIST v1.1 and iRECIST criteria, as presented in the consensus guidelines for iRECIST by Seymour et al 2017[92] is reproduced in Table 40.

Table 39 Comparison of RECIST v1.1 and immune-related response criteria (2009)

Category	RECIST v1.1	Immune-related response criteria
Measurement of tumour burden	Unidimensional	Bidemensional
Target lesions	Maximum, 5	Maximum, 15 index lesions
New lesion	Results in progressive disease at first appearance	Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point
Complete response	Disappearance of all target and nontarget lesions Nodes must regress to <10 mm short axis No new lesions Confirmation required	
Partial response	≥30% decrease in tumour burden compared with baseline Confirmation required	≥50% decrease in tumour burden compared with baseline Confirmation required
Progressive disease	≥20% + 5-mm absolute increase in tumour burden compared with nadir Appearance of new lesions or progression of nontarget lesions	≥25% increase in tumour burden compared with baseline, nadir, or reset baseline - If an increase in tumour burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment New lesions added to tumour burden Confirmation required
Stable disease	Neither partial response nor progressive disease	

RECIST v1.1= Response Evaluation Criteria in Solid Tumors
Source: Hodi et al 2016,[91] Table 1

Table 40 Comparison of RECIST v1.1 and iRECIST criteria (2017)

Criteria	RECIST v1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST
iUPD=unconfirmed progression; iUPD=confirmed progression; iCR=complet response; iPR=partial response; iSD=stable disease; RECIST v1.1= Response Evaluation Criteria in Solid Tumours version 1.1
Source: Seymour et al 2017[92]

9.2 Appendix 2: ERG testing of proportional hazards for CheckMate 214 trial data

The validity of the PH assumption within the trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms (OS, [redacted]33; PFS, [redacted]34, [redacted]35, [redacted]36, [redacted]37). For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

9.2.1 Overall survival (intermediate/poor risk group)

The H-H plot for the OS data from the CheckMate 214 trial is provided in [redacted]33. The data are distributed fairly evenly about the linear trend line; however the linear regression model estimates a statistically significant deviation from the origin of 0.016 (95% CI: 0.013 to 0.019), suggesting that the PH assumption may not hold for OS data from the CheckMate 214 trial.

[redacted]33

OS=overall survival
Source: Company clarification response B1

9.2.2 IRRC-assessed progression-free survival (intermediate/poor risk group, primary definition)

Visual inspection of [redacted]34 indicates that the PH assumption may not hold for IRRC-assessed PFS (primary definition) data from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.052 (95% CI: 0.044 to 0.059).

[redacted]34

IRRC=independent radiology review committee; PFS=progression-free survival
Source: Company clarification response B1

9.2.3 IRRC-assessed progression-free survival (intermediate/poor risk group secondary definition)

Visual inspection of [redacted]35 indicates that the PH assumption may not hold for IRRC-assessed PFS (secondary definition) data from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and to underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.080 (95% CI: 0.070 to 0.090).

[redacted]35

IRRC=independent radiology review committee; PFS=progression-free survival
Source: Company clarification response B1

9.2.4 Investigator-assessed progression-free survival (intermediate/poor risk group primary definition)

Visual inspection of [redacted]36 indicates that the PH assumption may not hold for investigator-assessed PFS (primary definition) data from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and to underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.125 (95% CI: 0.109 to 0.141).

[redacted]36

PFS=progression-free survival
Source: Company clarification response B1

9.2.5 Investigator-assessed progression-free survival (intermediate/poor risk group, secondary definition)

Visual inspection of [redacted]37 indicates that the PH assumption may not hold for investigator-assessed PFS (secondary definition) data from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and to underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.130 (95% CI: 0.113 to 0.146).

[redacted]37

PFS=progression-free survival
Source: Company clarification response B1

9.2.6 Overall survival (intermediate risk group)

Visual inspection of [redacted]38 indicates that the PH assumption may not hold for OS data for the intermediate-risk group from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.032 (95% CI: 0.028 to 0.036).

[redacted]38

OS=overall survival
Source: Company clarification response B1

9.2.7 Overall survival (poor risk group)

Visual inspection of [redacted]39 indicates that the PH assumption holds for OS data for the poor-risk group from the CheckMate 214 trial. The linear model appears to fit the data well. The linear model also estimates a statistically non-significant deviation from the origin of -0.01 (95% CI: -0.022 to 0.003).

[redacted]39

OS=overall survival
Source: Company clarification response B1

9.2.8 IRRC-assessed progression-free survival (intermediate risk group primary definition)

Visual inspection of [redacted]42 indicates that the PH assumption may not hold for investigator-assessed PFS data (secondary definition) for the intermediate-risk group from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.046 (95% CI: 0.038 to 0.054).

[redacted]40

IRRC=independent radiology review committee; PFS=progression-free survival
Source: Company clarification response B1

9.2.9 IRRC-assessed progression-free survival (poor risk group primary definition)

Visual inspection of [redacted]42 indicates that the PH assumption may not hold for investigator-assessed PFS data (secondary definition) for the poor-risk group from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.149 (95% CI: 0.115 to 0.183).

[redacted]41

IRRC=independent radiology review committee; PFS=progression-free survival
Source: Company clarification response B1

9.2.10 Investigator-assessed progression-free survival (intermediate risk group secondary definition)

Visual inspection of [redacted]42 indicates that the PH assumption may not hold for investigator-assessed PFS data (secondary definition) for the intermediate-risk group from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.134 (95% CI: 0.115 to 0.152).

[redacted]42

PFS=progression-free survival
Source: Company clarification response B1

9.2.11 Investigator-assessed progression-free survival (poor risk group secondary definition)

Visual inspection of [redacted]42 indicates that the PH assumption may not hold for investigator-assessed PFS data (secondary definition) for the poor-risk group from the CheckMate 214 trial. The linear model appears to overestimate mortality in the NIVO+IPI arm of the trial in the early and late stages of the trial, and underestimate mortality in the intervening period. The linear model also estimates a statistically significant deviation from the origin of 0.196 (95% CI: 0.160 to 0.232).

[redacted]43

PFS=progression-free survival
Source: Company clarification response B1

9.3 Appendix 3: Baseline characteristics of patients in the CheckMate 214 and COMPARZ trials

Table 41 Baseline characteristics, CheckMate 214 trial and COMPARZ trial

Characteristic	CheckMate 214 – intermediate / poor-risk		CheckMate 214 – all patients		COMPARZ	
	NIVO+IPI (n=425)	Sunitinib (n=422)	NIVO+IPI (n=550)	Sunitinib (n=546)	Pazopanib (n=557)	Sunitinib (n=553)
Median age, years (range)	62 (26-85)	61 (21-85)	62 (26-85)	62 (21-85)	61 (18-88)	62 (23-86)
Male, n (%)	314 (74)	301 (71)	413 (75)	395 (72)	398 (71)	415 (75)
KPS, n (%)						
90 or 100	[redacted]	[redacted]	[redacted]	[redacted]	416 (75)	423 (76)
70 or 80	[redacted]	[redacted]	[redacted]	[redacted]	141 (25)	130 (24)
<70	[redacted]	[redacted]	[redacted]	[redacted]	0	0
Risk category, n (%)†						
Favourable	(0)	(0)	125 (23)	124 (23)	151 (27)	152 (27)
Intermediate	334 (79)	333 (79)	334 (61)	333 (61)	322 (58)	328 (59)
Poor	91 (21)	89 (21)	91 (17)	89 (16)	67 (12)	52 (9)
Unknown	n/a	n/a	n/a	n/a	17 (3)	21 (4)
Lactate dehydrogenase, n (%)						
≤1.5× ULN	[redacted]	[redacted]	NR §	NR §	517 (93)	524 (95)
>1.5× ULN	[redacted]	[redacted]	NR §	NR §	40 (7)	29 (5)
Not reported	[redacted]	[redacted]	NR §	NR §	n/a	n/a
Number of involved organs, n (%)						
1	90 (21)	84 (20)	123 (22)	118 (22)	117 (21)	108 (20)
≥2	335 (79)	338 (80)	427 (78)	428 (78)	439 (79)	445 (80)
Missing	-	-	-	-	1 (<1)	0
Most common metastatic sites, n (%)						
Lung	293 (69)	295 (70)	380 (69)	371 (68)	424 (76)	425 (77)
Lymph node	191 (45)	215 (51)	248 (45)	268 (49)	223 (40)	247 (45)
Liver	89 (21)	89 (21)	99 (18)	109 (20)	86 (15)	110 (20)
Bone	85 (20)	89 (21)	99 (18)	104 (19)	110 (20)	85 (15)
Prior nephrectomy, n (%)	384 (90.4)	378 (89.6)	507 (92.2)	500 (91.6)	459 (82)	465 (84)
Prior radiation therapy, n (%)	52 (12.2)	52 (12.3)	63 (11.5)	70 (12.8)	46 (8)	42 (8)
Prior systemic therapy, n (%):						
Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Neo-adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

KPS= Karnofsky performance status; NR=not reported; ULN=upper limit of normal

† Risk assigned using International Metastatic RCC Database Consortium in the CheckMate 214 trial and Memorial Sloan-Kettering Cancer Center in the COMPARZ trial

§ In the CSR it is reported the data are presented in Table S.3.3A; this table was not made available with the CSR provided to the ERG

Source: CS, adapted from Table 6, CheckMate 214 CSR, adapted from Tables 3 and Motzer et al 2013, adapted from Supplementary Table S3.

9.4 Appendix 4: Subsequent treatment received by intermediate and poor risk groups in the CheckMate 214 trial

9.4.1 Subsequent cancer therapy summary for patients who were censored for IRRC-assessed PFS due to subsequent therapy

The subsequent anti-cancer therapies received by patients who were censored for PFS per IRRC due to subsequent anti-cancer therapy are summarised for intermediate and poor risk patients separately in Table 42. Patients may be counted more than once in any given anti-cancer therapy category.

Table 42 Subsequent therapy summary for patients who were censored for IRRC-assessed PFS (primary definition) by risk group

Subsequent therapy, n (%)	Intermediate risk		Poor risk	
	NIVO+IPI (n=334)	Sunitinib (n=333)	NIVO+IPI (n=91)	Sunitinib (n=89)
Any subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]
ALK/EGFR tyrosine kinase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CTLA-4	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD-1	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD-L1	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
IFN	[redacted]	[redacted]	[redacted]	[redacted]
IFN-α	[redacted]	[redacted]	[redacted]	[redacted]
IL-2	[redacted]	[redacted]	[redacted]	[redacted]
Investigational immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy – chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy – experimental drugs	[redacted]	[redacted]	[redacted]	[redacted]

ALK=anaplastic lymphoma kinase; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; EGFR=epidermal growth factor receptor; IFN=interferon; IL=interleukin; IRRC=independent radiology review committee; NIVO+IPI=nivolumab + ipilimumab; PD-1=programmed death receptor-1; PD-L1=programmed death receptor ligand-1; PFS=progression-free survival
Source: Company response to ERG clarification letter, question A1c, Tables 5 and 6

9.4.2 Summary of subsequent cancer therapy received on disease progression

A breakdown of subsequent treatment received on disease progression in the CheckMate 214 trial is presented for intermediate risk patients and poor risk patients separately in Table 43.

Table 43 Subsequent cancer therapy received in CheckMate 214 by risk group

Subsequent therapy, n (%)	Intermediate risk		Poor risk	
	NIVO+IPI (n=334)	Sunitinib (n=333)	NIVO+IPI (n=91)	Sunitinib (n=89)
Any subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]
ALK/EGFR tyrosine kinase inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CTLA-4	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD-1	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD-L1	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
IFN	[redacted]	[redacted]	[redacted]	[redacted]
IFN-α	[redacted]	[redacted]	[redacted]	[redacted]
IL-2	[redacted]	[redacted]	[redacted]	[redacted]
Investigational immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy – chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy – experimental drugs	[redacted]	[redacted]	[redacted]	[redacted]

ALK=anaplastic lymphoma kinase; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; EGFR=epidermal growth factor receptor; IFN=interferon; IL=interleukin; NIVO+IPI=nivolumab + ipilimumab; PD-1=programmed death receptor-1=PD-L1, programmed death receptor ligand-1

Source: Company response to ERG clarification letter, question A14, Tables 31 and 32

9.5 Appendix 5: Supportive evidence: CheckMate 016 trial

CheckMate 016 is a Phase I non-randomised, open-label ongoing study investigating various combinations of nivolumab-based therapy in patients with advanced RCC with a clear-cell component and a KPS ≥80%. It originally included five arms including nivolumab in combination with ipilimumab (using three different dosing schedules), sunitinib and pazopanib. Three arms were closed due to dose-limiting toxicity. The remaining two arms were variations of nivolumab in combination with ipilimumab, known as N3I1, which is the dosing schedule subsequently adopted in CheckMate 214 and N13I, which is the dosing schedule that has been adopted for treating melanoma. A total of 47 patients were assigned to each study arm (N1I3 and N3I1). Further details of the dosing schedules are presented in Table 44.

Table 44 Comparison of the NIVO+IPI doses licensed (or expected to be licensed) for treating RCC and melanoma, as also investigated in the CheckMate 016 trial

Dose schedule	Description of dose schedule
N3I1 (This is the dose anticipated to be indicated for treating RCC)	The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks. The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab
N1I3 (This is the dose indicated for treating melanoma)	The recommended dose is 1 mg/kg nivolumab administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with 3 mg/kg ipilimumab administered intravenously over 90 minutes This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks. The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab

Source: Draft summary of product characteristics, CS, Appendix C.1.

There were a number of key differences in terms of the patient populations of the CheckMate 016 trial and CheckMate 214 trial. Most notably, most patients were in the favourable risk (45%) or intermediate risk (49%) categories and risk was determined using the MSKCC model. Furthermore, not all patients were treatment naïve for advanced RCC, the proportions being 53% in the N3I1 arm and 48% in the N1I3 arm. A total of 26 (55.3%) patients in the N3I1 arm and 19 (40.4%) patients in the N1I3 arm received subsequent systemic therapy.

The primary outcome of the CheckMate 016 trial was to assess the safety and tolerability of NIVO+IPI in order to determine the maximum tolerated dose. Data presented in the CS are based on a median follow-up of 37.7 months in the N3I1 arm and 36.0 months in the N1I3 arm, after the latest analysis at June 2017 data cut-off. At this data-cut, 5 (10.6%) patients in the N3I1 arm and 3 (6.4%) patients in the N1I3 arm were still on treatment.

Proportionately more patients in the N3I1 arm had a complete response than in the N1I3 arm (10.6% versus 2.6%) with a longer duration of response (median 105 weeks versus 79.4 weeks). However, OS rates at 24-months were marginally lower in the N3I1 arm compared with the N13I arm (66% versus 72%, median OS was not reached in either arm) as was median PFS (7 months versus 9.4 months). No statistical significance testing has been reported for these outcomes.

Compared to the N1I3 dose, fewer patients treated at the N3I1 dose experienced Grade 3 to 4 TRAEs. The most common Grade 3 to 4 TRAEs with possible immune-mediated aetiology in the N3I1 and N1I3 arms, respectively, were gastrointestinal (4.3% and 23.4%) and hepatic (6.4% and 21.3%). The selected N3I1 regimen taken forward to the CheckMate 214 trial was in acknowledgement of the more favourable toxicity profile.

9.6 Microsoft Excel revisions made by the ERG to the company's model

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

Instructions for modifying the updated company model

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

1. Paste the following table into a new sheet named 'ERG switches' and name the switches with the modification names

Revision #	Name	Switch	Description	Instructions
Correction	Mod_A	0	Company correction to ipilimumab treatment cost calculation	Use switch (0,1)
R1	-	-	Remove immunotherapeutic survival effect from company model	Set Controls!F100 to "No"
R2	Mod_B	0	ERG remodelled OS estimates from CheckMate 214	Use switch (0,1)
R3	Mod_C	0	ERG remodelled PFS estimates from CheckMate 214	Use switch (0,1)
R4	-	-	Remove TTD stopping rule from company model	Set Controls!F40 to "No"
R5	Mod_D	0	ERG remodelled TTD estimates from CheckMate 214 (without stopping rule)	Use switch (0,1)
R6	Mod_E	0	Assume pazopanib TTD=sunitinib TTD	Use switch (0,1)
R7	Mod_F	0	Model 7 utility values including all three main effects	Use switch (0,1)
R8	-	-	Use CheckMate 214 proportions for subsequent treatments	Set Controls!F113 to "CheckMate 214"
R9	Mod_H	0	Add administration costs for suntinib and pazopanib	Use switch (0,1)

2. Move sheets from *1182_ ERG additional model data.xlsx* into the model

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

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
Correction	Mod_A	Treatment Costs and Resources	M22	=((E22/G22)*F22)*IF(Mod_A=0,1,0)+(((E22/G22)*F22)*L22)*IF(Mod_A=1,1,0)
Correction	Mod_A	Treatment Costs and Resources	M23	=((E23/G23)*F23)*IF(Mod_A=0,1,0)+(((E23/G23)*F23)*L22)*IF(Mod_A=1,1,0)
R2 ERG remodelled OS estimates from CheckMate 214	Mod_B	OS	BP30: BP2152	=IFERROR(IF(cont.OS_curve_fit_depend="Dependent",BM30,IF(cont.OS_curve_fit_depend="Independent",BJ30,"ERROR")),0)*IF(Mod_B=0,1,0)+'ERG Time to event'!E11*IF(Mod_B=1,1,0)
R2 ERG remodelled OS estimates from CheckMate 214	Mod_B	OS	BQ30: BQ2152	=IFERROR(IF(cont.OS_curve_fit_depend="Dependent",BN30,IF(cont.OS_curve_fit_depend="Independent",BK30,"ERROR")),0)*IF(Mod_B=0,1,0)+'ERG Time to event'!H11*IF(Mod_B=1,1,0)
R2 ERG remodelled OS estimates from CheckMate 214	Mod_B	OS	BS30: BS2152	=(IF(BP30>p_cont.IO_1L.prop,BP30,BS29*(1-BR29)))*IF(Mod_B=0,1,0)+'ERG Time to event'!E11*IF(Mod_B=1,1,0)
R2 ERG remodelled OS estimates from CheckMate 214	Mod_B	OS	BT30: BT2152	=(IF(BQ30>p_cont.IO_2L.prop*p_st_sunit_to_nivo*$BT$26,BQ30,BT29*(1-BR29)))*IF(Mod_B=0,1,0)+'ERG Time to event'!H11*IF(Mod_B=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R2 ERG remodelled OS estimates from CheckMate 214	Mod_B	OS	BU30: BU2152	=(IF(BQ30>p_cont.IO_2L.prop*p_st_pazo_to_nivo*$BU$26,BQ30,BU29*(1-BR29)))*IF(Mod_B=0,1,0)+'ERG Time to event'!H11*IF(Mod_B=1,1,0)
R3 ERG remodelled PFS estimates from CheckMate 214	Mod_C	PFS	CN31: CN2153	=MIN(IF(cont.PFS_curve_fit_depend="Dependent",CL31,CJ31),OS!BW30)*IF(Mod_C=0,1,0)+'ERG Time to event'!F11*IF(Mod_C=1,1,0)
R3 ERG remodelled PFS estimates from CheckMate 214	Mod_C	PFS	CO31: CO2153	=MIN(IF(cont.PFS_curve_fit_depend="Dependent",CM31,CK31),OS!BX30)*IF(Mod_C=0,1,0)+'ERG Time to event'!I11*IF(Mod_C=1,1,0)
R5 ERG remodelled TTD estimates from CheckMate 214 (without stopping rule)	Mod_D	TTD	CQ28: CQ2150	=IF(AND(cont.stopping_rule_Y_N="Yes",TTD!BH28>cont.stopping_rule_length),0,MIN(IF(cont.TTD_curve_fit_depend="Dependent",CN28,CK28),OS!BW30))*IF(Mod_D=0,1,0)+'ERG Time to event'!G11*IF(Mod_D=1,1,0)
R5 ERG remodelled TTD estimates from CheckMate 214 (without stopping rule)	Mod_D	TTD	CR28: CR2150	=MIN(IF(cont.TTD_curve_fit_depend="Dependent",CO28,CL28),OS!BX30)*IF(Mod_D=0,1,0)+'ERG Time to event'!J11*IF(Mod_D=1,1,0)
R6 Assume pazopanib TTD=sunitinib TTD	Mod_E	TTD	CS28: CS2150	=(CR28^p_TTD_pazoHR.vsunit)*IF(Mod_E=0,1,0)+CR28*IF(Mod_E=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R7 Model 7 utility values including all three main effects	Mod_F	PF Nivoipi	T19: T2105	=J19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_nivoipi+IF(cont.AE.utility.Nivo="Yes",TotalAEcycleQALYdecr_nivoipi,0))*IF(Mod_F=0,1,0)+J19*(cont.cycle_length_prop_yr*'ERG Utilities'!$B$11+IF(cont.AE.utility.Nivo="Yes",TotalAEcycleQALYdecr_nivoipi,0))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Nivoipi	U19: U2105	=(K19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_nivoipi)*IF(Mod_F=0,1,0)+(K19*cont.cycle_length_prop_yr*'ERG Utilities'!$B$12)*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Nivoipi	V19: V2105	=(L19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_nivoipi+IF(cont.AE.utility.Nivo="Yes",TotalAEcycleQALYdecr_nivoipi,0)))*IF(Mod_F=0,1,0)+(L19*(cont.cycle_length_prop_yr*'ERG Utilities'!$B$13+IF(cont.AE.utility.Nivo="Yes",TotalAEcycleQALYdecr_nivoipi,0)))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Nivoipi	W19: W2105	=(M19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_nivoipi+u_st_qaly_nivoipi*Q19)*IF(Mod_F=0,1,0)+(M19*cont.cycle_length_prop_yr*'ERG Utilities'!$B$14+u_st_qaly_nivoipi*Q19)*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Sunit	T19: T2105	=J19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_sunit+IF(cont.AE.utility.sunit="Yes",TotalAEcycleQALYdecr_sunit,0))*IF(Mod_F=0,1,0)+J19*(cont.cycle_length_prop_yr*'ERG Utilities'!$C$11+IF(cont.AE.utility.sunit="Yes",TotalAEcycleQALYdecr_sunit,0))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Sunit	U19: U2105	=K19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_sunit*IF(Mod_F=0,1,0)+K19*cont.cycle_length_prop_yr*'ERG Utilities'!$C$12*IF(Mod_F=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R7 Model 7 utility values including all three main effects	Mod_F	PF Sunit	V19: V2105	=L19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_sunit+IF(cont.AE.utility.sunit="Yes",TotalAEcycleQALYdecr_sunit,0))*IF(Mod_F=0,1,0)+L19*(cont.cycle_length_prop_yr*'ERG Utilities'!$C$13+IF(cont.AE.utility.sunit="Yes",TotalAEcycleQALYdecr_sunit,0))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Sunit	W19: W2105	=(M19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_sunit+u_st_qaly_sunit*Q19)*IF(Mod_F=0,1,0)+(M19*cont.cycle_length_prop_yr*'ERG Utilities'!$C$14+u_st_qaly_sunit*Q19)*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Pazo	T19: T2105	=J19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_pazo+IF(cont.AE.utility.pazo="Yes",TotalAEcycleQALYdecr_pazo,0))*IF(Mod_F=0,1,0)+J19*(cont.cycle_length_prop_yr*'ERG Utilities'!$D$11+IF(cont.AE.utility.pazo="Yes",TotalAEcycleQALYdecr_pazo,0))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Pazo	U19: U2105	=K19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_pazo*IF(Mod_F=0,1,0)+K19*cont.cycle_length_prop_yr*'ERG Utilities'!$D$12*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Pazo	V19: V2105	=L19*(cont.cycle_length_prop_yr*UTILITY_PFSonTx_pazo+IF(cont.AE.utility.pazo="Yes",TotalAEcycleQALYdecr_pazo,0))*IF(Mod_F=0,1,0)+L19*(cont.cycle_length_prop_yr*'ERG Utilities'!$D$13+IF(cont.AE.utility.pazo="Yes",TotalAEcycleQALYdecr_pazo,0))*IF(Mod_F=1,1,0)
R7 Model 7 utility values including all three main effects	Mod_F	PF Pazo	W19: W2105	=(M19*cont.cycle_length_prop_yr*UTILITY_PFSoffTx_pazo+u_st_qaly_pazo*Q19)*IF(Mod_F=0,1,0)+(M19*cont.cycle_length_prop_yr*'ERG Utilities'!$D$14+u_st_qaly_pazo*Q19)*IF(Mod_F=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R9 Add administration costs for suntinib and pazopanib	Mod_H	Treatment Costs and Resources	E57	=0*IF(Mod_H=0,1,0)+164*IF(Mod_H=1,1,)
R9 Add administration costs for suntinib and pazopanib	Mod_H	Treatment Costs and Resources	E58	=0*IF(Mod_H=0,1,0)+164*IF(Mod_H=1,1,)

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

ERG STA REPORT ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Addendum to STA report prior to Appraisal Committee meeting

Confidential until published

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

Completed 4th May 2018

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Following the submission of the Evidence Review Group (ERG) report and prior to the Appraisal Committee meeting, the National Institute for Health Care Excellence (NICE) requested some additional information from the ERG. The additional information requested is presented in this addendum.

2 END-OF-LIFE CRITERIA

2.1 Median overall survival

In the original ERG report (Table 37) the ERG summarised median overall survival (OS) of patients with advanced renal cell carcinoma (RCC) treatment with tyrosine kinase inhibitors (TKIs), using the same six studies used by the company in its submission. The six studies comprised four real world studies and two randomised controlled trials (RCTs):

1. Heng et al 2013:[1] an international retrospective study to validate the International Metastatic RCC Database Consortium (IMDC) model for assessing risk

2. Gore et al 2015:[2] an international prospective one-armed global-expanded access trial of sunitinib

3. Kubackova et al 2015:[3] a retrospective population study using registration data from the Czech Republic to compare the IMDC with the Memorial Sloan Kettering Cancer Center (MSKC) model for assessing risk

4. de Groot et al 2016:[4] a retrospective and prospective population study using registry data from the Netherlands to evaluate the uptake and use of targeted therapies, examine factors associated with the prescription of targeted therapies and study their effectiveness in terms of OS

5. CheckMate 214 trial:[5] the pivotal international phase III RCT of nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib

6. COMPARZ trial (Motzer et al 2014):[6] an international phase III noninferiority RCT of pazopanib versus sunitinib.

NICE requested that further to Table 37 in the ERG report that the ERG perform some further investigation on the included studies to detail any uncertainty reported and explain the variation in the median OS.

Table 37 has been expanded upon here (Table 1). The table now reports 95% confidence intervals (CIs) alongside the median OS data. The ERG has included data for intermediate/poor risk from de Groot et al 2016 (the same data reported by the company in their submission to be for all patients) although it should be noted that for the prospective cohort, the intermediate risk group includes patients with favourable risk disease. Finally, the ERG has also included additional data on intermediate/poor risk disease from the recently published phase II CABOSUN study[7] of carbozantinib versus sunitinib as initial therapy for metastatic RCC.

Table 1 Overall survival reported for patients treated with VEGFR-TKIs in studies of advanced RCC

Study	Model for assessing risk	Median OS (95% CI), months		
		Intermediate risk	Poor risk	Intermediate/ poor risk
Sunitinib				
Heng et al 2013	IMDC	22.5 (18.7–25.1)	7.8 (6.5–9.7)	-
Gore et al 2015*	IMDC	18.9 (17.4–20.2)	6.2 (5.6–6.7)	-
Kubackova et al 2015†	IMDC Modified MSKCC	(a) 24.8 (19.8–29.8) (b) 28.5 (20.1–36.8)	(a) 9.3 (5.1–13.5) (b) 10.6 (6.3–14.8)	-
de Groot et al 2016§	Modified MSKCC	(i) 14.6 (11.5–16.0) (ii) 16.6 (10.1–NE)	(i) 6.1 (4.9–7.7) (ii) 6.5 (3.4–10.0)	(i) 9.1 (7.2–11.1) (ii) 10.1 (7.2–13.8)
CheckMate 214¥	IMDC	[redacted]	[redacted]	26.0 (22.1–NE)
COMPARZ	MSKCC	26.1 (20.7–31.6)	7.7 (5.4–11.9)	-
CABOSUN	IMDC	-	-	21.2 (16.3–27.4)
Pazopanib				
COMPARZ	MSKCC	26.9 (23.1–35.6)	9.9 (7.3–12.3)	-

CI=confidence interval; IMDC= The International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Center; NE=not estimable; NR=not reached; OS-overall survival
* The company only report a median OS of 19.0 months from this study
† Only data reported using the IMDC model are reported by the company, data reported here are reported using (a) IMDC and (b) MSKCC model. The ERG notes that Using the IMDC model, 54.1% of MSKCC poor risk patients were reclassified as intermediate risk and 20.2% of MSKCC intermediate-risk patients were reclassified as favourable risk
§ Data for the poor risk group and all patients are reported by the company; data reported here are taken from the published paper (Table 4) and are the median OS from (i) retrospective 2008 to 2010 cohort and (ii) prospective 2011 to 2013 cohort. Data for intermediate risk group for (ii) - and therefore all patients in this cohort - include some patients with favourable risk prognosis
¥ Data are immature and from post-hoc analyses requested by the ERG and should be treated with caution. Lower confidence interval in the intermediate risk group is 25.8 months
Source: adapted from CS, Table 19

Table 1 shows that for patients with intermediate/poor risk disease in the de Groot study, median OS was 9.1 months in the retrospective cohort and 10.1 months in the prospective cohort. Patients were classified using the modified MSKCC in the Groot study. Using the IMDC model to classify risk, median OS for intermediate/poor risk disease patients ranged from 21.2 months in the CABOSUN study to 26.0 months in the CheckMate 214 trial.

Estimates of OS with TKIs varied across studies for patients with intermediate risk disease, from 18.9 months to 24.8 months in three studies with risk classified by the IMDC model ([redacted]) and from 14.6 months to 28.5 months in

three studies with risk classified by the MSKCC model. There was less variability in the estimates of median OS for poor risk patients, ranging from 6.2 months to [redacted] in three studies with risk classified by the IMDC model and 6.1 months to 10.6 months in three studies with risk classified by the MKSCC model.

The study by de Groot et al includes the most pessimistic estimates of median OS. This study included patients who were not treated with any systemic therapy although the OS results presented by the company and ERG are only for those who did receive first-line treatment with sunitinib. It is noticeable that compared to the other studies, including the CheckMate 214 trial, this study included a relatively high proportion of patients aged ≥65, patients with non-clear cell disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 and lactate dehydrogenase levels above the upper limit of normal (see Appendix). These are all characteristics which may lead to a patient having a poorer prognosis and, therefore, reduced OS.

Gore et al also presented relatively pessimistic estimates of median OS. This study also included a relatively high proportion of patients with non-clear cell disease and ECOG PS ≥2. This is also the oldest study considered by the company and ERG, being conducted between June 2005 and December 2007. These could all be factors that have resulted in a lower median OS. It should also be noted that the median follow-up was 13.6 months in this study, which is the shortest follow-up reported by any of the study authors who reported this information. It is possible, therefore, that with longer follow-up, estimates of median OS would be higher.

It should also be noted that the studies by de Groot et al and Gore et al include patients who received a TKI as second-line or later treatment, as does the study by Heng et al. All other studies only include patients receiving a TKI as first-line treatment.

Ignoring the results from de Groot et al and Gore et al results in much less variability in estimates of median OS for patients treated with a TKI using the IMDC model. Median OS for intermediate/poor risk disease ranges from 21.2 months to 26.0 months. For intermediate risk patients, the range is 22.5 months to 24.8 months using the IMDC model (two studies, [redacted]) and 26.1 months to 28.5 months using the MKSCC model (two studies). For poor risk patients the range is 7.8 months to 9.3 months using the IMDC model (three studies) and 7.7 months to 10.6 months using the MKSCC model (two studies).

The ERG notes that Kubackova et al have estimated OS using both prognostic risk models. Using the IMDC resulted in more pessimistic estimates of OS than using the MKSCC model (Table 1). In this study, 54.1% of MSKCC poor risk patients were reclassified as intermediate risk using the IMDC model and 20.2% of MSKCC intermediate-risk patients were reclassified as favourable risk using the IMDC model.

2.2 Pooled estimate of median overall survival

NICE requested that the ERG consider pooling the data from the studies in a meta-analysis. This would entail considering all the studies as if they were all single-arm studies.

Standard meta-analysis methods (i.e. inverse variance methods) require data to be normally distributed either on the scale it is measured on or transformed. Therefore, it is not possible to pool medians using standard methods.

The ERG therefore examined other possible methods to obtain an overall point estimate and estimated uncertainty of median OS. The ERG is only aware of one published method for pooling median survival times from single arm studies.[8] As this method has not been widely adopted, the ERG would need to investigate the suitability of the method and, if appropriate, learn how to implement the method. Unfortunately, it has not been feasible for the ERG to complete this task in the time available before the Appraisal Committee meeting.

However, even if it had been technically possible to conduct this task, the ERG has other concerns that mean it may not be appropriate to pool the data from all of the studies. These concerns relate to differences in trial and patient characteristics. Even if the studies by de Groot et al and Gore et al were excluded from a meta-analysis, other notable differences in characteristics exist (see Appendix), namely:

- Differences in the prognostic model used to determine risk disease
- Differences in study follow-up
- Differences in PS
- Differences in the proportions of patients with ≥2 metastatic sites
- Differences in the location of metastatic sites.

2.3 Weighted median overall survival

As described in the ERG report, the ERG considers the proportion of intermediate risk patients seen in clinical practice is likely to be lower than were included in the CheckMate 214 trial and the proportion of patients with poor risk disease greater in clinical practice than in the CheckMate 214 trial. The proportion of patients with intermediate and poor risk disease from studies referred to in Section 2.1 of this addendum report are presented in Table 2. Based on clinical advice it received, the ERG considers that the estimated proportions reported in the Heng et al study are more likely to be reflective of the proportions seen in clinical practice (52% intermediate risk and 30% poor risk).

NICE requested that the ERG estimated a weighted average median OS for intermediate/poor risk patients to reflect clinical practice. The ERG was able to obtain a weighted median OS for patients receiving sunitinib in the CheckMate 214 to reflect UK clinical practice. The ERG applied sampling weights to the K-M data so that estimates of median OS represented a patient population of intermediate and poor risk groups in a ratio of 50:30. The analysis was conducted using standard survival analysis commands in Stata 14 (stset and stsum) to obtain the median survival time (as these commands are capable of taking sampling weights into consideration). The weighted median OS calculated for this dataset was 21.8 months. Standard survival analysis methods do not allow the calculation of confidence intervals for median survival estimates for weighted K-M data. As far as the ERG is aware, there is no widely accepted method for obtaining confidence intervals for weighted median survival times.

Table 2 The number and proportions of patients by risk disease reported in studies of advanced RCC

Prognostic status	Population based studies						RCTs		
	Heng et al 2013 [a]	Gore et al 2015 [a]	Kubackova et al 2015 [a]	Kubackova et al 2015 [b]	de Groot et al 2016 [bi]	de Groot et al 2016 [bii]	CheckMate 214 [a]	COMPARZ trial	CABOSUN study [a]
Patients with known risk, n	849	4065	495	495	282	109	1096	1072	157
Favourable risk, n (%)	157 (18)	988 (24)	109 (22)	60 (12)	0	65 (60)*	249 (23)	303 (28)	0
Intermediate risk, n (%)	440 (52)	2188 (54)	309 (62)	302 (61)	145 (51)		667 (61)	650 (61)	63 (81)
Poor risk, n (%)	252 (30)	889 (22)	77 (16)	133 (27)	137 (49)	44 (40)	180 (16)	119 (11)	15 (29)

IMDC= The International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Center; RCT=randomised controlled trial
a IMDC
b MSKCC or modified MSKCC
i 2008 to 2010 cohort
ii 2011 to 2013 cohort
* patients with favourable risk disease and intermediate risk disease were combined in the same risk group in the 2011 to 2013 cohort of de Groot et al

2.4 Mean overall survival

NICE requested that the ERG present mean values for OS for all the published studies it included in Table 37 of its report, if available. No mean values for OS have been reported in any of the published studies. As previously reported in the ERG report, mean OS for intermediate/poor risk patients was 37.3 months in the CheckMate 214 trial.

2.5 ERG conclusions

Based on evidence from four real world studies and three RCTs, patients with poor risk disease have a short life expectancy of less than 24 months. Only one study of first-line TKI treatment has estimated a median OS for intermediate risk patients using the IMDC model, the model which is specified as defining risk in the NICE scope. This study found median OS to be 24.8 months. [redacted]

The population for whom NIVO+IPI is indicated is patients with intermediate/poor risk disease. In the CheckMate 214 trial, median OS in this patient population was 26 months. However, the ERG has found that the weighted average, assuming there to be 50% patients with intermediate risk disease and 30% with poor risk disease (instead of 61% and 16% respectively as in the CheckMate 214 trial) is 21.8 months. This is similar to the unweighted average OS reported for sunitinib in the recent phase II CABOSUN study (21.2 months).

3 COST EFFECTIVENESS ANALYSES

NICE informed the ERG that NHS England has noted that, contrary to the company submission, if recommended, NIVO+IPI would displace (rather than replace) first-line therapy. Therefore, people who progress would then receive one of the current first-line options. The ERG was therefore requested to perform a scenario analysis.

3.1 Scenario analysis assumptions

The ERG has investigated the effect on the ICER per QALY gained of assuming that treatment with NIVO+IPI would displace rather than replace treatment with sunitinib and pazopanib. In this scenario, treatment with sunitinib and pazopanib move into the second-line setting following treatment with NIVO+IPI and replace other second-line treatments included in the company model. The ERG has assumed in this scenario that, after treatment with NIVO+IPI, 50% of patients who receive second-line treatment (30% of all patients who progress) will receive sunitinib and 50% (30% of all patients who progress) will receive pazopanib. Patient access scheme (PAS) discounts for first-line treatment with sunitinib and pazopanib are also applied in the second-line setting.

The ERG has applied this assumption to the company's corrected base case and to the ERG's revised base case. Assumptions about treatment proportions following treatment with sunitinib and with pazopanib in the first-line setting remain unchanged according to the relevant base case (Table 3). The impact on the ICERs per QALY gained of incorporating the assumption that treatment with NIVO+IPI would displace treatment with sunitinib and pazopanib is shown in Table 4 (versus sunitinib) and Table 5 (versus pazopanib).

Table 3 Sources of assumed proportions for subsequent therapies in base case and scenario: company and ERG

	Base case subsequent therapy proportions following:		**Scenario subsequent therapy proportions following:**	
	NIVO+IPI	**Sunitinb or pazopanib**	**NIVO+IPI**	**Sunitinb or pazopanib**
Company original base case	Clinical opinion[1]	Clinical opinion[1]	-	-
Company corrected base case	Clinical opinion[1]	Clinical opinion[1]	50% sunitinib 50 % pazopanib	Clinical opinion[1]
ERG revised base case	CheckMate 214	CheckMate 214	50% sunitinib 50 % pazopanib	CheckMate 214

[1]50% Axitinib and 50% Cabozantinib

3.2 Cost effectiveness results from the scenario analysis

In the company corrected base case, assuming treatment with sunitinib and pazopanib in the subsequent-line setting after treatment with NIVO+IPI decreases the ICER per QALY gained versus sunitinib by £8,015 to £20,053. In the ERG revised base case, assuming treatment with sunitinib and pazopanib in the subsequent-line setting after treatment with NIVO+IPI decreases the ICER per QALY gained versus sunitinib by £4,897 to £33,255.

In the company corrected base case, assuming treatment with sunitinib and pazopanib in the subsequent-line setting after treatment with NIVO+IPI decreases the ICER per QALY gained versus pazopanib by £9,497 to £18,525. In the ERG revised base case, assuming treatment with sunitinib and pazopanib in the subsequent-line setting after treatment with NIVO+IPI decreases the ICER per QALY gained versus pazopanib by £4,676 to £32,062.

Table 4 Cost effectiveness NIVO+IPI versus sunitinib (PAS for nivolumab and ipilimumab)

Base case scenario	ICER per QALY gained	
	Base case subsequent therapy assumptions	Sunitinib and pazopanib 2nd line after NIVO+IPI*
Company original base case	***£28,865***	**-**
Company corrected base case	***£28,068***	***£20,053***
ERG revised base case (R2, R3, R5, R7, R8, R9)	***£38,152***	***£33,255***

ICER=incremental cost effectiveness ratio; PAS=Patient-access scheme; QALY=quality adjusted life year
*relevant base case assumptions maintained for subsequent therapies following first-line treatment with sunitinib or pazopanib. See Table 3

Table 5 Cost effectiveness NIVO+IPI versus pazopanib (PAS for nivolumab and ipilimumab)

Base case scenario	ICER per QALY gained	
	Base case subsequent therapy assumptions	Sunitinib and pazopanib 2nd line after NIVO+IPI*
Company original base case	***£28,819***	**-**
Company corrected base case	***£28,022***	***£18,525***
ERG revised base case (R2, R3, R5, R6, R7, R8, R9)	***£36,738***	***£32,062***

ICER=incremental cost effectiveness ratio; PAS=Patient-access scheme; QALY=quality adjusted life year
*relevant base case assumptions maintained for subsequent therapies following first-line treatment with sunitinib or pazopanib. See Table 3

4 REFERENCES

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5 APPENDIX: CHARACTERISTICS OF THE STUDIES INCLUDED IN THE END-OF-LIFE ANALYSIS

Study characteristics extracted by the ERG are summarised in Table 6. The patient characteristics are summarised in Table 7.

Table 6: Study characteristics

Characteristic	Heng et al 2013	Gore et al 2015	Kubackova et al 2015	de Groot et al 2016		CheckMate 214	COMPARZ	CABOSUN
Treatment received	TKI (n=1028)	Sunitinib (n=4543	Sunitinib (n=495)	282 (44%) patients received first-line sunitinib 309 (48%) patients received no systemic therapy at all	110 (47%) patients received first-line sunitinib 94 (40%) patients received no systemic therapy at all	Control arm, sunitinib (ITT, n=546; intermediate/ poor risk, n=546) Treatment crossover not allowed	Pazopanib (n=557) or sunitinib (n=553)	Control arm, sunitinib (n=78); all patients had intermediate/ poor risk disease Treatment crossover not allowed
Tool used to assess risk	IMDC	IMDC	IMDC and Modified MSKCC	Modified MSKCC	Modified MSKCC	IMDC	MSKCC	IMDC
Study type	retrospective	prospective	retrospective	prospective	retrospective	Phase III RCT	Phase III RCT	Phase II RCT
Geographic location	13 centres in 5 countries	50 countries	Czech Republic population registry	Netherlands population registry (42 of 51 hospitals)	Netherlands population registry (25 of 32 hospitals)	184 sites in 28 countries	14 countries in North America, Europe, Australia, and Asia	77 centres in the United States
Dates of study	August 2008 to January 2011	June 2005 to December 2007	2006 to 2013	January 2008 to December 2010	January 2011 to June 2013	October 2014 to February 2016	August 2008 to September 2011	July 2013 to April 2015
Previous Tx for advanced RCC permitted?	Previous immune-therapy was allowed (Patients treated with front-line mTOR inhibitors were excluded	Yes	No	Yes	Yes	No	No	No
Follow-up, median (range) months	16.3 (7.4–30.6)	13.6	-	≥36	-	25.2	-	35.4 (31.4–40.4)
Duration of Tx, median (range) months	-	7.5	4.8 (0.1–39.7)	-	-	7.8 with sunitinib	Pazopanib: 8.0 (0–40) Sunitinib: 7.6 (0–38)	3.1 (2.0–8.2) with sunitinib

IMDC= The International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Center; RCT=randomised controlled trial

Table 7: Baseline characteristics

Characteristic	Heng et al 2013	Gore et al 2015	Kubackova et al 2015	de Groot et al 2016		CheckMate 214		COMPARZ		CABOSUN
	TKI* (n=1028)	Sunitinib (n=4543)	Sunitinib (n=495)	Cohort i (n=645) Sunitinib 1L (n=282)	Cohort ii (n=233) Sunitinib 1L (n=109)	Sunitinib intermediate / poor risk (n=422)	Sunitinib ITT (n=546)	Pazopanib (n=557)	Sunitinib (n=553)	Sunitinib (n=78)
Median age, years (range)	-	59.0 (19–89)	64 (35–83)	66 (23-93)	66 (27-93)	61 (21-85)	62 (21-85)	61 (18-88)	62 (23-86)	64 (57-71)
Age ≥60 years	564 (55%)	-	-	-	-	-	-	-	-	-
Age ≥65	-	1485 (33%)	-	Sunitinib 1L: 120 (43%)	Sunitinib 1L: 45 (42%)	[redacted]	-	-	-	-
Male	765 (74%)	3364 (74%)	336 (68%)	408 (66%)	161 (73%)	301 (71%)	395 (72%)	398 (71%)	415 (75%)	57 (73%)
Clear-cell histology	-	4010 (88%)	469 (95%)	354 (57%) Sunitinib 1L: 204 (72%)	152 (69%) Sunitinib 1L: 81 (74%)	422 (100%)	546 (100%)	557 (100%)	553 (100%)	78 (100%)
KPS 90 or 100 / ECOG PS 0	KPS <80: 261 (27%)	ECOG 0: 1868 (41%)	KPS <80: 69 (14%)	WHO PS ≤1: 430 (69%) Sunitinib 1L: 248 (88%)	WHO PS ≤1: 178 (81%) Sunitinib 1L: 100 (92%)	KPS 90-100: [redacted]	KPS 90-100: [redacted]	KPS 90-100: 416 (75%)	KPS 90-100: 423 (76%)	ECOG 0: 36 (46%)
KPS 70 or 80 / ECOG PS 1	-	ECOG 1: 1949 (43%)	-			KPS 70-80: [redacted]	KPS 70-80: [redacted]	KPS 70-80: 141 (25%)	KPS 70-80: 130 (24%)	ECOG 1: 32 (41%)
KPS <70 / ECOG PS ≥2	-	ECOG 2: 634 (14%)	-	WHO 2-4: 191 (31%) Sunitinib 1L: 34 (12%)	WHO 2-4: 42 (19%) Sunitinib 1L: 9 (8%)	KPS <70: [redacted]	KPS <70: [redacted]	0	0	ECOG 2: 10 (13%)
LDH ≤1.5× ULN	634 (88%)	-	435 (88%)	372 (60%)	179 (81%)	[redacted]	- [§]	517 (93%)	524 (95%)	-
LDH >1.5× ULN	87 (12%)	-	60 (12%)	249 (40%)	42 (19%)	[redacted]	- [§]	40 (7%)	29 (5%)	-
1 metastatic site	233 (23%)	-	213 (43%)	206 (33%)	87 (39%)	84 (20%)	118 (22%)	117 (21%)	108 (20%)	26 (33%)
≥2 metastatic sites	791 (77%)	-	282 (57%)	415 (67%)	134 (61%)	338 (80%)	428 (78%)	439 (79%)	445 (80%)	52 (67%)
Lung metastases	-	3469 (76%)	-	448 (72%)	147 (67%)	295 (70%)	371 (68%)	424 (76%)	425 (77%)	54 (69%)
Lymph node metastases	-	2333 (51%)	-	-	-	215 (51%)	268 (49%)	223 (40%)	247 (45%)	42 (54%)
Liver metastases	176 (20%)	1236 (27%)	-	112 (18%)	46 (21%)	89 (21%)	109 (20%)	86 (15%)	110 (20%)	20 (26%)
Bone metastases		1593 (35%)	-	228 (37%)	63 (29%)	89 (21%)	104 (19%)	110 (20%)	85 (15%)	30 (38%)
Central nerve system/brain metastases	99 (10%)	338 (7%)	-	50 (8%) Sunitinib 1L: 21 (7%)	16 (7%) Sunitinib 1L: 8 (7%)	-	-	-	-	2 (3%)

Characteristic	Heng et al 2013	Gore et al 2015	Kubackova et al 2015	de Groot et al 2016		CheckMate 214		COMPARZ		CABOSUN
	TKI* (n=1028)	Sunitinib (n=4543)	Sunitinib (n=495)	Cohort i (n=645) Sunitinib 1L (n=282)	Cohort ii (n=233) Sunitinib 1L (n=109)	Sunitinib intermediate / poor risk (n=422)	Sunitinib ITT (n=546)	Pazopanib (n=557)	Sunitinib (n=553)	Sunitinib (n=78)
Prior immunotherapy for aRCC	245 (24%)	-	n/a	-	-	n/a	n/a	n/a	n/a	n/a
Prior antiangiogenic for aRCC†	-	440 (10%)	n/a	-	-	n/a	n/a	n/a	n/a	n/a
Prior cytokine for aRCC	-	3096 (68%)	n/a	-	-	n/a	n/a	n/a	n/a	n/a
Prior radiation therapy	-	-	-			52 (12%)	70 (13%)	46 (8%)	42 (8%)	-
Prior Adjuvant	-	-	-	-	-	[redacted]	[redacted]	-	-	-
Prior Neo-adjuvant	-	-	-	-	-	[redacted]	[redacted]	-	-	-
Prior nephrectomy	798 (78%)	4044 (89%)	410 (83%)	-	-	378 (90%)	500 (92%)	459 (82%)	465 (84%)	60 (77%)

'-'=not reported; aRCC=advanced renal cell carcinoma; ECOG=Eastern Cooperative Oncology Group; IMDC=The International Metastatic Renal Cell Carcinoma Database Consortium; KPS= Karnofsky performance status; LDH=lactate dehydrogenase; MSKCC=Memorial Sloan Kettering Cancer Center; n/a=not applicable; PS=performance status; Sunitinib 1L=sunitinib, first-line; ULN, upper limit of normal; WHO=World Health Organization

i 2008 to 2010 retrospective cohort

ii 2011 to 2013 prospective cohort

* In Heng et al 2013, 844 (82%) patients were treated with sunitinib, other TKIs included sorafenib, bevacizumab and axitinib

† included sorafenib and bevacizumab

§ In the CSR it is reported the data are presented in Table S.3.3A; this table was not made available with the CSR provided to the ERG

Notes:

The KPS, ECOG PS and WHO PS scores do not equate exactly but are presented above as approximations

All data are reported as a proportion of available data (with missing data excluded from the calculations)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the Liverpool Reviews and Implementation Group (LRIG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm on 19 April** 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 committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74: "All modelled individuals who remain progression-free and on first-line treatment after 5 years also transit to the 'PFS Off 1L Tx' health state"	This is only applicable to NIVO+IPI patients: "All modelled individuals on the NIVO+IPI arm who remain progression-free…"	Factual inaccuracy that could mislead the reader.	Text amended for clarity on page 74: "Additionally, all modelled individuals on the NIVO+IPI arm who remain progression-free…"
Page 74: "Terminal care is a temporary health state that captures cost and utility"	There are no utility changes currently modelled for the terminal care state.	Factual inaccuracy that could mislead the reader.	Text amended for clarity on page 74: "Terminal care is a temporary health state that captures additional cost ~~and utility~~ associated with 8 weeks…"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94: “It should also be noted that both the Checkmate 003 and Checkmate 010 trials included multiple dosing regimens, which may influence the shape of the results shown in Figure 7”	“… included multiple nivolumab monotherapy dose regimens ….” Ipilimumab is not included in these trials.	Factual inaccuracy that could mislead the reader.	Text amended for clarity on page 93: “It should also be noted that both the CheckMate 003 and CheckMate 010 trials included multiple nivolumab monotherapy dose regimens, which may influence the shape of the results shown in Figure 7.”
Page 94: “mortality rates do not approach general mortality rates in any of these trials during the reported study period” & Page 97: “All three indicate decreasing hazards over time, but none approach zero mortality risk during the trial period”	None of the trials have follow-up longer than when we are expecting this immunotherapeutic effect to become apparent in the model. This should be considered as part of Section 5.4.3	Factual inaccuracy that could mislead the reader.	Not a factual error. No change made.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104: “Figure 17 Company log-logistic OS curve (no immunotherapeutic effect)”	“Figure 17 Company log-logistic curve OS curve without general mortality cap included (mortality rates cannot be lower than those of the age-matched general population)”	Factual inaccuracy that could mislead the reader.	Text amended for clarity on page 106: “This means that~~, if an immunotherapeutic effect does not exist, then~~ patients treated with either NIVO+IPI or sunitinib will have a lower risk of death than the general population after 20 years. The ERG notes that the company has included a cap in the model to ensure that OS mortality rates do not fall below general population mortality rates. This means that there is a strict change to general population mortality at around 20 years, which indicates that all patients who have lived at least 20 years after beginning treatment with either NIVO+IPI or sunitinib will no longer be at risk from advanced RCC and should be considered cured of the disease. The company does not acknowledge this assumption in its submission.”

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105: "Figure 18 Company OS log-logistic curves including general mortality rate assumption (with immunotherapeutic effect)"	"…(with 100% probability of immunotherapeutic effect)"	Factual inaccuracy that could mislead the reader.	Caption amended to: "Figure 1 Company OS log-logistic curves including general mortality rate assumption (with 100% probability of immunotherapeutic effect)"
Page 106: "Figure 20 Weekly mortality rates in the company model: without an immunotherapeutic effect"	"…Weekly mortality rates using log-logistic curves for OS" Currently in the model, a cap is applied so that weekly mortality rates cannot be lower than those of the age-matched general population. This statement in the ERG report does not take that into account.	Factual inaccuracy that could mislead the reader.	Caption amended to: "Figure 20 Weekly mortality rates in the company log-logistic model: without an immunotherapeutic effect"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107: “The assumption of no immunotherapeutic effect for treatment with NIVO+IPI (or for treatment with nivolumab in the second-line setting) leads to mortality rates lower than general mortality after 20 years for patients treated with both NIVO+PI and with sunitinib”	Currently in the model, a cap is applied so that weekly mortality rates cannot be lower than those of the age-matched general population. This statement in the ERG report does not take that into account. Sentence is incorrect and should read, “leads to mortality rates equal to the general mortality after 20 years…”	Factual inaccuracy that could mislead the reader.	Text amended on page 108 for clarity: “The assumption of no immunotherapeutic effect for treatment with NIVO+IPI (or for treatment with nivolumab in the second-line setting) leads to mortality rates lower than general mortality after 20 years for patients treated with both NIVO+PI and with sunitinib (the company’s mortality cap for the assumption of no immunotherapeutic effect does not apply in the combined base case model).”

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113: “However, during TA417, the submitting company did not investigate the effect of treatment status on utility estimates”	As part of TA417 post-submission communications, the company investigated a stepwise selection approach for utility analysis, including treatment status as well as progression status and treatment arm (explanatory variables and interaction terms). The best fitting model from this stepwise selection process was the same as that used in the base case by the company.	Factual inaccuracy that could mislead the reader.	Text amended on page 114 to read: However, during TA417, the ~~submitting company did not investigate the effect of treatment status on utility estimates and~~ company’s base case utility model included only the effects of treatment and progression status.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115: “Using only the company’s modelling of the assumption of ‘no immunotherapeutic effect on OS’ results in an increase in the ICER per QALY gained of £5,958 to £34,026 for treatment with NIVO+IPI versus sunitinib and of £5,945 to £33,967 for treatment with NIVO+IPI versus pazopanib.” ERG Revision 1	For this scenario, we believe that the ERG has only removed the immunotherapeutic effect for 1L NIVO+IPI and not for 2L nivolumab, as these are two separate switches in the model (‘Controls’ F100 and F104). If both switched are set to “No”, the ICER versus sunitinib is £33,912 and versus pazopanib is £33,831.	Factual inaccuracy that could mislead the reader.	Text amended on page 115: Using only the company’s modelling of the assumption of ‘no immunotherapeutic effect on OS’ results in an increase in the ICER per QALY gained of ~~£5,958~~ £5,323 to ~~£34,026~~ £33,392 for treatment with NIVO+IPI versus sunitinib and of ~~£5,945~~ £5,359 to ~~£33,967~~ £33,381 for treatment with NIVO+IPI versus pazopanib. Values amended in row 3 (R1), Table 34, page 125 of the CS and in Table 1 of the confidential appendix Values amended in row 3 (R1), Table 35, page 126 and in Table 2 of the confidential appendix

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 125: ERG revised base case Also referenced in Section 1.12 (page 21), Section 5.7 (page 127) and Section 7.2 (page 131)	It appears that although stated in the revised base case as being included (ERG revised base case [R2, R3, R5, R7, R8, R9]), R8, using CheckMate 214 subsequent therapy proportions, has not been included in the final ICER. Clinical opinion is set as the base case in the shared ERG model, and conditional formatting in cell O12 of the ERG switches tab has been applied incorrectly. Including R8 in the ERG base case as described in the ERG report gives an ICER of £38,152 versus sunitinib and £36,738 versus pazopanib.	Factual inaccuracy, resulting in change to the ERG revised base case.	Text amended on page 21 and page 125 to: "…treatment status and progression status; subsequent treatment from the CheckMate 214 trial; and administration costs for treatment with sunitnib and pazopanib. ~~estimates of costs associated with IMAEs~~ . Values amended in final row 3 (ERG base case), Table 34, page 126 and in table 1 of the confidential appendix Values amended in final row 3 (ERG base case), Table 35, page 127 and in table 2 of the confidential appendix Text amended in Section 5.7 (page) 128 to: "The ERG's revised base case yields an ICER of ~~£39,970~~ £38,152 per QALY gained for the

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			comparison of treatment with NIVO+IPI versus treatment with sunitinib, which is ~~£11,901~~ £10,083 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are ~~higher~~ lower ~~(+£1,093~~ -£775) than…" "The ERG's revised base case yields an ICER of ~~£38,543~~ £36,738 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with pazopanib, which is ~~£10,522~~ £8,716 higher than the company's corrected base case. The ERG's revised base case generates incremental costs that are lower ~~(£622~~ - £2,490) than…" Text amended in Section 7.2 (page 132) to:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			"The ERG's revised base case yields an ICER of ~~£39,970~~ £38,152 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with sunitinib, which is ~~£11,901~~ £10,083 higher than the company's corrected base case. The ERG's revised base case yields an ICER of ~~£38,543~~ £36,738 per QALY gained for the comparison of treatment with NIVO+IPI versus treatment with pazopanib, which is ~~£10,522~~ £8,716 higher than the company's corrected base case. "

Issue 2 Factual inaccuracies stemming from company Document B

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80, Table 21: Drug costs – ipilimumab total cost per week.	After correcting for the error described in Section 5.4.1 of the ERG report, the ipilimumab cost per cycle is [redacted].	Clarification – impact on base case ICER as described in Section 5.4.1 of the ERG report	Symbol added to ipilimumab cost per week Footnote added to Table 21, page 81: "† This value was updated by the company to [redacted] after it identified a calculation error"
Page 80, Table 21: Drug costs – vials per admin and total cost per week. These inaccuracies below are from previous iterations of the model that were not correctly updated after new model inputs, and have no impact on the model results. It is only these noted items in the document B that are effected, as the model contains the correct and latest inputs. As these reported table inaccuracies are now in the ERG report, we wanted to highlight these for clarity.	Nivolumab and ipilimumab vials per admin and ipilimumab cost per week are incorrectly reported in the company submission. Using the method of moments, nivolumab uses 1.64 and 2.01 100mg and 40mg vials, respectively, and ipilimumab uses 0.02 and 1.98 200mg and 50mg vials, respectively. The sunitinib cost per cycle is £674.84.	Clarification – no impact on model or results	Values amended in Table 21, page 81. Additional footnote to Table 21 added: "Note, where there are discrepancies between the CS and the company model, figures in this table reflect those used in the company model"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82, Table 23: Subsequent therapy drug costs – nivolumab cost per cycle	Nivolumab cost per cycle is incorrectly reported in the company submission. This should be [redacted]	Clarification – no impact on model or results	Table 23, page 83 amended as requested
Page 82, Table 24: Resource use total	The total costs per health state are incorrectly reported in the company submission. The total for PFS should be £20.68, and the total for PPS should be £71.38.	Clarification – no impact on model or results	Table 24, page 83 amended as requested
Page 83: "the unit costs were applied to cycle event probabilities from the CheckMate 214 trial to produce AE cycle costs of £4.24 and £15.63 for NIVO+IPI and sunitinib respectively"	The AE cost per cycle for sunitinib should read as £15.21.	Clarification – no impact on model or results	Text amended on page 84 as requested

Issue 3 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, Page 54 and Page 56: Academic in confidence (AIC) marking has not been applied correctly.	Information on discontinuations due to TRAEs should be marked up as AIC information, as well as all reported ICERs.	These changes will maintain the correct AIC nature of the data.	The data are taken from Table 14 of the company submission (document B) and are not marked as AIC. However, we have now marked the data as AIC on pages 11, 54 and 56

Issue 4 Typographical grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47: “The ERG concurs that a difference in PFS of 3.2 months is likely to be clinically meaningful although”	Suggest either remove or complete this sentence	ERG’s intended meaning is unclear.	Text deleted