NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

# 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 (CDF review of TA581) [ID3880]

**Contents:**

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Bristol-Myers Squibb**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Kidney Cancer UK *(endorsed by patient expert, Jennifer Vaughan)*
   b. NCRI-ACP-RCP-RCR

4. **Evidence Review Group report** prepared by **Liverpool Reviews & Implementation Group (LRiG)**

5. **Evidence Review Group – factual accuracy check**

6. **Public Health England Study Report**

7. Technical engagement response from **Bristol-Myers Squibb**

8. **Technical engagement response & expert statement from experts:**
   a. Dr Natalie Charnley, clinical expert, nominated by NCRI-ACP-RCP-RCR
   b. Dr Richard Griffiths, clinical expert, nominated by BMS
   c. Sophie Ann-Scott, patient expert, nominated by Kidney Cancer UK

9. Evidence Review Group critique of company response to technical engagement prepared by **Liverpool Reviews & Implementation Group (LRiG)**

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

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Cancer Drugs Fund Review of TA581

# Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

## Company evidence submission for committee

## September 2021

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID3880 CDF Review NIVO+IPI 1L RCC Company Submission 100921** | **1.0** | **Yes/no** | **10 September 2021** |



# Contents





# Tables and figures





# Cancer Drugs Fund review submission

## A.1 Background

- Nivolumab with ipilimumab (NIVO+IPI) is recommended for use within the Cancer Drugs Fund (CDF) as an option for adults with untreated advanced renal cell carcinoma (RCC) that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. It is recommended only if the conditions in the managed access agreement for NIVO+IPI are followed

- The committee accepted that NIVO+IPI had the potential to be cost-effective, but more evidence was needed to address the clinical uncertainties
- The committee highlighted the following key uncertainties during the original appraisal:
  - The long-term benefit of NIVO+IPI, including overall survival (OS), and its relationship with immunological effect, and whether a proportion of people are 'cured'
  - The subsequent treatments used in clinical practice
  - The proportion of people with intermediate- and poor- risk RCC in clinical practice
- The committee recognized that clinical data, specifically OS for CheckMate 214, were immature. The trial is ongoing, and the committee agreed that more data could resolve the key clinical uncertainties, including the relationship between immunological effect and response to NIVO+IPI. Additional evidence on subsequent treatments could also be collected from real-world data to resolve the uncertainties

## A.2 Key committee assumptions

Key committee assumptions as per the terms of engagement are presented in Table 1, with BMS comments added below key assumptions.



**Table 1: Key committee assumptions as per the terms of engagement**

| Area | Committee preferred assumptions |
|---|---|
| Population | The key trial supporting the appraisal (CheckMate 214) stratified people by prognostic score as defined by the International Metastatic Renal Carcinoma Database Consortium (IMDC) scoring system. The trial included 180 people with poor-risk, 667 people with intermediate-risk and 249 people with favourable-risk untreated renal cell carcinoma.<br>The company focused its submission to NICE on the intermediate and poor risk score subgroups to align with the expected marketing authorisation. The committee concluded that the combined intermediate- or poor-risk group is appropriate for decision-making, although recognised the uncertainty around the proportion of people with poor and intermediate risk scores in practice.<br>**Adults with intermediate- or poor-risk untreated advanced renal cell carcinoma are the relevant population for the CDF review. Data collected through SACT should be used to inform the proportion of people with poor- and intermediate-risk disease.**<br>BMS acknowledges that SACT data is intended to reflect clinical practice in England but does not agree that this data source should be used to inform the proportion of people with poor- and intermediate-risk disease. Justification for this is provided in Section A.6.2.1. |
| Comparators | The relevant comparators are sunitinib and pazopanib. Cabozantinib and tivozanib are also recommended for untreated advanced renal cell carcinoma but were not part of NHS clinical practice at the time of the original appraisal.<br>After hearing from clinical experts, the committee concluded that pazopanib and sunitinib are the relevant comparators and can be considered clinically equivalent. This includes for time-to-stopping treatment, which the company assumed was slightly longer for pazopanib. Committee preferred that the time-to-stopping treatment for pazopanib was the same as sunitinib.<br>**The company should present clinical and cost-effective evidence for nivolumab with ipilimumab compared to sunitinib and pazopanib. The company should also ensure the time-to-stopping treatment is the same for both pazopanib and sunitinib.**<br>BMS agrees with this. |
| Definition of progression-free survival (PFS) | CheckMate 214 used two definitions of PFS. The primary definition censored people going onto other treatments before disease progression. The secondary definition included these people. The committee shared the ERG's concern that the primary PFS definition represented a form of informative censoring. This is because people who need subsequent treatment before progression may systematically differ between the two treatment arms.<br>The committee concluded that the secondary definition of PFS was most appropriate for decision-making. The assessment of PFS was also discussed and the committee agreed with the company's use of independent radiology review committee (IRRC) assessed PFS as |



| Area | Committee preferred assumptions |
|---|---|
| | opposed to trial investigator assessed which was preferred by the ERG.<br>**The company should use the IRRC assessed and secondary definition of PFS to inform the economic model.**<br>BMS acknowledges the co-primary endpoint in the CM-214 study was IRRC assessed PFS per primary definition; however, in light of preference by ERG and NICE committee, BMS agrees to use the secondary definition in the economic model for this assessment. |
| Treatment switching | An interim data cut (August 2017) from CheckMate 214 showed that nivolumab with ipilimumab improved progression-free and overall survival compared to sunitinib giving hazard ratios of 0.76 and 0.63 respectively. Because of this, the trial was stopped early.<br>Committee were aware that trials stopped early for benefit can overestimate the benefit. In the subsequent interim analysis (August 2018) people were allowed to switch to the treatment arm from the comparator which the company did not adjust for. Committee acknowledged that this likely biased the hazard ratio towards the null but concluded that the data remained too immature to establish the long-term effect of treatment, and the impact of treatment switching.<br>**The company should use more mature survival data from CheckMate 214 and fully explore the most appropriate approach to adjust for treatment switching.**<br>As agreed at the kick-off call with NICE and the ERG, due to the small patient numbers switching treatment, creating additional uncertainty in survival extrapolations by adjusting for crossover would be inappropriate. Therefore, this adjustment is not included. |
| Extrapolating survival data | Committee were aware that follow up was short (median 25.2 months) and survival data were immature. The company extrapolated survival outcomes by fitting parametric curves to the observed data from the August 2018 data cut (a log-normal distribution for OS, cubic spline for PFS and [redacted] for time-to-stopping treatment).<br>The ERG preferred to use a piecewise model, using KM data followed by an exponential curve from the point where the cumulative hazard plots showed a constant hazard rate. The ERG did this for all three survival outcomes.<br>Considering the 'cure', committee questioned whether an exponential extrapolation was appropriate for PFS but this modelling had minimal impact on the ICER.<br>The OS extrapolation had the largest impact on the ICER. Committee noted that the log-normal distribution resulted in a small proportion of people not explicitly modelled as cured, being cured as the log-normal hazard rates meet general mortality population rates at about 20 years. The company provided an updated ERG analysis in response to consultation but committee had concerns about the fitting of the survival curve in the comparator arm.<br>In the absence of long-term data the committee could not determine which curve was more appropriate but deemed both to be plausible. |



| Area | Committee preferred assumptions |
|---|---|
| | **The company should use updated survival data from CheckMate 214 to fully explore the most appropriate method to extrapolate survival outcomes.**<br>BMS agrees with this |
| Immunological effect | Some people in the economic model assumed a death rate equal to that of the general population and were effectively 'cured'.<br>The company based the probability of this on durable response; the number of people whose disease achieved a complete or partial response at the time of the August 2017 data cut. The committee were concerned that this was defined post hoc, and the company did not present evidence associating a relationship between durable response and overall survival.<br>The company assumed that 15% of those randomised to the nivolumab with ipilimumab arm would be cured. Clinical experts stated they'd expect 20% of people on treatment to have an immunological effect, but it is not known how this would translate into life expectancy. The committee considered the company's 15% estimate to be implausible because fewer than 15% of people were still on treatment at the end of follow-up.<br>The committee thought that people who have had long-term immunotherapy would not live as long on average as people without advanced renal cell cancer. Committee suggested a more reasonable assumption would be to apply standardised mortality ratios to general population mortality rates.<br>The committee concluded that the underlying assumptions for an immunological effect were speculative and also that the modelling was flawed because there was no structural link in the model between an immunological effect and progression-free survival. Without this the ERG thought it was inappropriate to assume that those who had a durable response were also the people that lived beyond 9 years (and assumed general mortality rates).<br>**Longer-term data from CheckMate 214 should inform assumptions about OS and immunological response, including the relationship between the two.**<br>BMS agrees with this. Data are presented in Section A.7.3.1 related to the immunological effect NIVO+IPI has on untreated advanced RCC. |
| Stopping rule | The company assumed that people stopped taking nivolumab with ipilimumab after 5 years, even if their disease had not progressed and they continued to benefit from the treatment. Neither the marketing authorisation, nor CheckMate 214 included a stopping rule and committee considered its appropriateness. The company did not explore the effect of a stopping rule on clinical outcomes, and in the model, it impacted costs only. The committee were not satisfied that the treatment effect would continue beyond stopping treatment.<br>The committee concluded that it was not appropriate to include a stopping rule for decision-making because its effect on clinical outcomes were untested. |



| Area | Committee preferred assumptions |
|---|---|
| | **The company should not include a stopping rule in the updated economic model.**<br>BMS agrees with this |
| Dosing regimen | CheckMate 214 used a weight-based dosing regimen, but by the committee's second meeting the regulators had changed the dosing to a flat dose of nivolumab given less frequently. Committee discussed whether these two dosing regimens would be equally effective and concluded that it was appropriate to use the new standard flat-dosing regimen.<br>**The company should use the flat-dosing regimen for incorporating treatment costs into the model.**<br>BMS agrees with this |
| Quality of life | Utility values were derived from EQ-5D-3L data collected in CheckMate 214. The model assumed that people would have different values based on treatment arm and whether they were on treatment, but the committee recognised that disease progression would also impact utility values. They felt that disease progression would worsen quality of life.<br>The company provided an updated regression model to reflect this, but it did not include patients whose disease had progressed on treatment.<br>Committee concluded that the model should include estimates of quality of life reflecting whether the disease had progressed but agreed that the cost-effectiveness estimates were unlikely to be sensitive to the utility values.<br>**The company should use more mature quality of life data from CheckMate 214 and ensure that it reflects differences by treatment arm, whether the person is on treatment, and disease progression status.**<br>BMS agrees with this |
| Subsequent treatments | The subsequent treatments in Checkmate 214 did not reflect clinical practice. The company used clinical opinion to determine the expected costs of subsequent treatments in the NHS. The ERG used the distribution of treatments of subsequent treatments from CheckMate 214.<br>In the absence of an analysis reflecting costs and clinical benefits from subsequent treatments used in the NHS, the committee preferred the ERG approach.<br>In response to consultation the company included the distribution of subsequent therapies seen in CheckMate 214 but did not adjust for treatment switching.<br>**The company should explore the most appropriate modelling of subsequent treatments, supported by data collected through SACT.**<br>As stated by the ERG in Section 3.17 of Final Appraisal Document, BMS will use CheckMate 214 subsequent therapies in the model base |



| Area | Committee preferred assumptions |
|---|---|
| | case as these are linked to the trial's clinical outcomes. SACT subsequent therapy data will be used as a scenario only. |
| Most plausible ICER | The cost-effectiveness results are commercial in confidence because they include the confidential commercial arrangements for subsequent therapies. Committee accepted some ERG changes to the company's analysis which were: removing the benefit from any immunological effect, removing the stopping rule, using the secondary definition of investigator-assessed PFS updated to the 2018 data cut, assuming equivalent time-to-stopping treatment for both comparators and including progression status in the utility regression.<br>This resulted in an ICER that was above the £20,000-£30,000 per QALY gained, but committee recognised that the lack of more mature data made the long-term outcomes very uncertain.<br>The company proposed a commercial arrangement for a CDF recommendation, and this brought the ICERs down to £20,000-£30,000 per QALY gained when using the different possible survival curves.<br>**The committee agreed that nivolumab demonstrated plausible potential to be cost-effective considering the company's proposed commercial arrangement.** |
| End of life | Nivolumab with ipilimumab does not meet the end-of-life criteria.<br>BMS agrees with this |
| **Key:** CDF, Cancer Drugs Fund; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; IMDC, the International Metastatic Renal Carcinoma Database Consortium; IRRC, independent radiology review committee; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIVO+IPI, nivolumab with ipilimumab; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SACT, systemic anti-cancer therapy dataset. | |

## A.3 Other agreed changes

The only other changes presented in this reappraisal are those related to the corrections in the cost-effectiveness model identified since the initial appraisal and the update to the confidential commercial arrangement for nivolumab.

## A.4 The technology

**Table 2: Technology being reviewed**

| | |
|---|---|
| **UK approved name and brand name** | Nivolumab with 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<br>– 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<br>• 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<br>– This pathway 'switches off' the immune response to tumour antigens, stopping production of activated T-cells in human malignancy<br>Nivolumab (NIVO) and ipilimumab (IPI) 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:<br>• NIVO stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour<br>• IPI 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<br>Nivolumab with ipilimumab (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/CE mark status** | An application was filed to the EMA on 7 November 2017 to allow nivolumab and ipilimumab to be used in combination with each other to treat untreated, advanced RCC in adults with intermediate- or poor-risk disease. CHMP opinion and MA were received in November 2018 and January 2019, respectively. |
| **Indications and any restriction(s) as described in the summary of product characteristics** | Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC. |
| **Method of administration and dosage** | Intravenous infusion.<br>NIVO 3 mg/kg plus IPI 1 mg/kg Q3W for four doses followed by NIVO 240 mg Q2W or 480 mg Q4W<br>Treatment should be continued as long as clinical benefit is observed or until the patient no longer tolerates treatment. |
| **Additional tests or investigations** | No additional tests or investigations are needed. |
| **List price and average cost of a course of treatment** | NIVO: £2,633.00 per 240 mg vial; £1,097.00 per 100 mg vial; £439.00 per 40 mg vial.<br>IPI: £15,000 per 200 mg vial; £3,750 per 50 mg vial |



| | |
|---|---|
| | Average patient cost of treatment: [redacted] Undiscounted estimate from deterministic base case economic analysis. |
| **Commercial arrangement (if applicable)** | There is a confidential commercial arrangement in place for NIVO and IPI approved by the Department of Health that is applicable to this appraisal. |
| **Date technology was recommended for use in the CDF** | 15 May 2019 |
| **Data collection end date** | The primary source for additional data collection was CheckMate 214. The CheckMate 214 data used to inform this submission is 60-month follow-up data from February 2021, an additional 30 months of minimum follow-up from the data used for final committee decision making in the initial appraisal. |
| **Key:** EMA, European Medicines Agency; CHMP, Committee for Medicinal Products for Human Use; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IPI: Ipilimumab; MA, marketing authorization; NIVO: Nivolumab; 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. | |

# A.5 Clinical effectiveness evidence

**Table 3: Primary source of clinical effectiveness evidence**

| **Study title** | **CheckMate 214 (NCT02231749)** |
|---|---|
| **Study design** | Multicentre, open-label, randomized Phase III study, minimum follow-up of 60 months |
| **Population** | Adults (≥ 18 years) with previously untreated advanced or metastatic RCC with a clear-cell component.<br>The primary analysis set comprised intermediate- and poor-risk patients. |
| **Intervention(s)** | NIVO 3 mg/kg IV combined with IPI 1 mg/kg IV Q3W for four doses then nivolumab 3 mg/kg IV Q2W |
| **Comparator(s)** | Sunitinib 50 mg PO once daily for 4 weeks followed by 2 weeks off, continuously |
| **Outcomes collected that address committee's key uncertainties** | In intermediate- and poor-risk patients:<br>• **OS**<br>• **PFS (IRRC assessed), secondary definition**<br>• ORR<br>• DoR<br>• **TTD**<br>• **Subsequent therapies** |



| Study title | CheckMate 214 (NCT02231749) |
|---|---|
| **Key:** DoR; duration of response; IRRC, independent radiological review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per os (orally); Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma; TTD, time to treatment discontinuation.<br>**Bold text** represents outcomes that the model incorporated. | |

**Table 4: Secondary source of clinical effectiveness data**

| Study title | SACT data cohort[1] |
|---|---|
| **Study design** | SACT data cohort, minimum follow-up 5 months |
| **Population** | Adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined by the International Metastatic Renal Cell Carcinoma Database Consortium criteria |
| **Intervention(s)** | Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for four doses, then nivolumab 240 mg IV Q2W or 480 mg IV Q4W |
| **Comparator(s)** | Not applicable |
| **Outcomes collected that address committee's key uncertainties** | • **Subsequent therapies** |
| **Key:** IV, intravenous; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; RCC, renal cell carcinoma; SACT, systemic anti-cancer therapy.<br>**Bold text** represents outcomes that the model incorporated. | |

# A.6 Key results of the data collection

Extended follow-up data reported from the CheckMate 214 trial (February 2021) includes a minimum of 60 months' follow-up. OS, progression-free survival (PFS), time-to-treatment discontinuation (TTD), overall response rate (ORR), duration of response (DoR) and subsequent therapy data were collected to address key uncertainties raised in the original submission. The updated data is consistent with those presented in the original submission and continues to provide long-term evidence to support the use of NIVO+IPI in RCC.

## A.6.1 CheckMate 214

All CheckMate 214 data reported within this submission relate to patients with intermediate- or poor-risk disease.



### *A.6.1.1 Overall survival*

A key uncertainty in the original submission was the long-term survival benefit associated with NIVO+IPI. The OS Kaplan–Meier (KM) plots from the latest data cut (60 months minimum follow-up) are presented in Figure 1, OS rates by treatment arm in Table 5, and summary statistics are presented in Table 6 by treatment arm (60-month data cut).

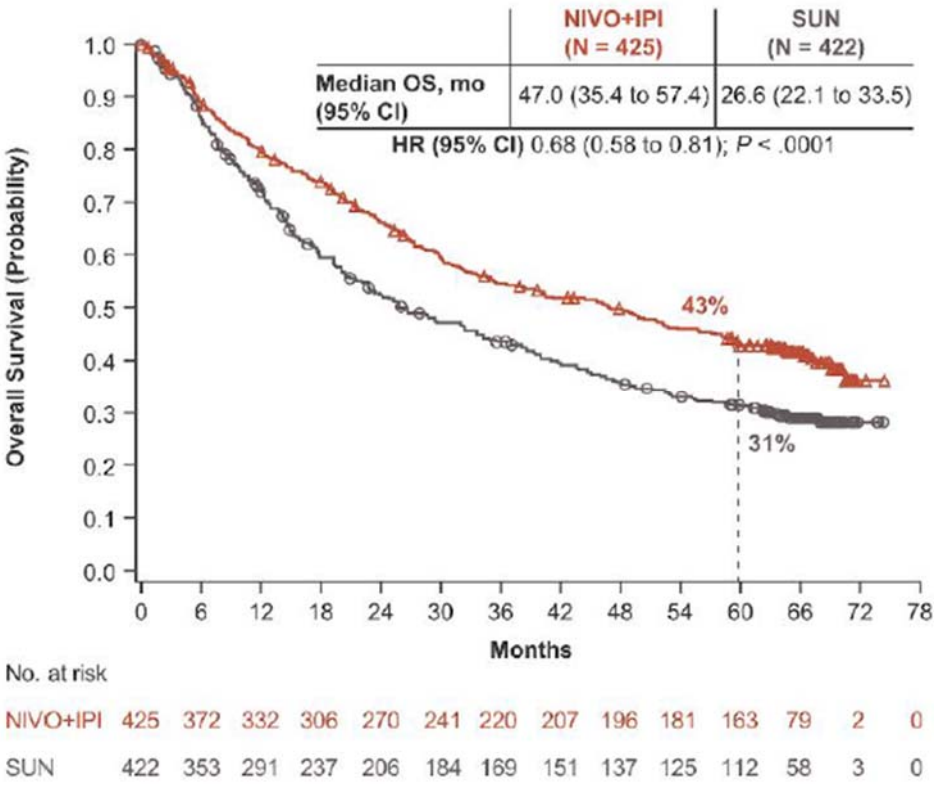
Separation of the KM curves occurs early (< 3 months) after randomization in favour of patients treated with NIVO+IPI, and this separation is sustained over the duration of follow-up (see Table 5 for OS rates by treatment arm). Throughout the study, patients treated with NIVO+IPI have consistently longer OS than patients treated with sunitinib across the observed study period.

Consistent with the earlier 30-month data cut, the 60-month data cut shows patients treated with NIVO+IPI continue to demonstrate a statistically significant improvement in OS compared with patients treated with sunitinib across the observed study period. In the original submission, though reached in the sunitinib arm, median OS for the NIVO+IPI arm had not been reached; in the 60-month data cut this is now realized at 47.0 (95% confidence interval [CI]: 35.4, 57.4) months compared with 26.6 (95% CI: 22.1, 33.5) months with sunitinib, a gain in median OS of 20 months for NIVO+IPI versus sunitinib and 5-year OS probabilities of 43% versus 31%. Moreover, the hazard ratio (HR) has remained stable across data cuts: 30-month data cut (HR: 0.66 [95% CI: 0.54, 0.80]), and 60-month data-cut (HR: 0.68 [95% CI: 0.58, 0.81]), confirming a sustained superior OS benefit in favour of NIVO+IPI compared with sunitinib. This evidence demonstrates that NIVO+IPI continues to have long-term OS benefit versus sunitinib, which is maintained with longer term follow-up.



**Figure 1: KM curve of OS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**




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

**Table 5: OS rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

| Timepoint in months | OS rates by treatment, % | |
|---|---|---|
| | NIVO+IPI | Sunitinib |
| 1 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] |
| 12[2] | 80.0 | 72.0 |
| 24[3] | 66.4 | 52.4 |
| 36 | [redacted] | [redacted] |
| 48[3] | 50.0 | 35.8 |
| 60 | 43.0 | 31.3 |
| Key: NIVO+IPI; nivolumab with ipilimumab; OS, overall survival. | | |



**Table 6: Summary statistics for OS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (30 and 60-month data cuts)**

| Data cut | Treatment | N | Events | Censors | Median (m; 95% CI) | HR (95% CI)[a] |
|---|---|---|---|---|---|---|
| 30-m | Sunitinib | 422 | 227 (54%) | [redacted] | 26.6 (22.1, 33.4) | Reference |
| | NIVO+IPI | 425 | 182 (43%) | [redacted] | NA (35.6, NA) | 0.66 (0.54–0.80) |
| 60-m | Sunitinib | 422 | [redacted] | [redacted] | 26.6 (22.1, 33.5) | Reference |
| | NIVO+IPI | 425 | [redacted] | [redacted] | 47.0 (35.4, 57.4) | 0.68 (0.58, 0.81) |

**Key:** CI, confidence interval, HR, hazard ratio; m, month; n, number.
**Notes:** [a] Hazard ratio estimated from stratified Cox proportional hazards model. A hazard ratio of less than 1 favours NIVO+IPI; a hazard ratio greater than 1 favours sunitinib.

### *A.6.1.2 ORR and duration of response*

In the original appraisal, the company assumed in the cost-effectiveness model that durable responses would lead to long-term survivorship. After the original appraisal, CheckMate 214 data have been published linking long-term survival to depth of response (maximum percent reduction from baseline in sum of target lesion diameters).[4] Using the 30-month data, and investigating the intention-to-treat (ITT) population, this study not only demonstrated that the increasing depth of response increased the probability of survival, but also that this relationship was distinct across treatment arms, with more NIVO+IPI patients having deeper responses, faster median time to response of > 50% tumour reduction and greater long-term OS benefits compared with those treated with sunitinib. The authors concluded that 'Overall, these results suggest that a depth of response threshold of > 50% may be a useful indicator of prolonged OS in aRCC patients treated with immune-oncology regimens'.[4]

Updated 60-month CheckMate 214 data demonstrated not only that a greater proportion of NIVO+IPI-treated patients respond (defined as complete or partial response), but also that response to NIVO+IPI was more durable than response to sunitinib. In the NIVO+IPI arm, with 60 months of follow-up, 42.1% (95% CI: 37.4%, 47.0%) of patients achieved a response (11.3% of patients with complete response),



compared with a 26.8% (95% CI: 22.6%, 31.3%) response rate in the sunitinib arm (2.1% of patients with a complete response). Figure 2 demonstrates the difference between arms in durability of these responses, where median DoR has not been met for NIVO+IPI while median DoR was previously reported for sunitinib as 19.7 months (95% CI: 15.4-25.0 months)3, reflecting a minimum gain of at least 40.3 months, based on minimum available follow-up of 60 months, (~3.4 years) in median DoR. Of those who responded in each arm at data cut off, [redacted] of patients in the NIVO+IPI arm had a response with duration of at least 60 months, compared with [redacted] of sunitinib patients. Similar to the data cut used in the submission and reported for data cuts in between[2,5], the NIVO+IPI arm has continued to have a higher complete response rate than the sunitinib arm (11.3% versus 2.1% with 60 months minimum follow-up), of which [redacted] had a duration of response of at least 60 months [redacted]. It should also be noted, of the patients who achieved a partial response, [redacted] of NIVO+IPI patients have a duration of response greater than 60 months compared with [redacted] in the sunitinib arm.

**Figure 2: CheckMate 214 – intermediate-/poor-risk patients, duration of response, 60-month follow-up**



### *A.6.1.3 Progression-free survival per IRRC*

The primary definition of PFS from CheckMate 214, which was part of the co-primary endpoint in the trial, used in the original company submission censored patients on receipt of subsequent therapy. However, the Evidence Review Group's (ERG) and committee's preferred analysis was to use the secondary definition of PFS, which does not censor on receipt of subsequent therapy. The final committee decision was to use the Independent Radiological Review Committee (IRRC)-assessed PFS (secondary definition) taken at the 18-month data cut (note at the time of the 30-month cut, PFS per IRRC was not available and did not form the basis of economic modelling in the updated analysis).[6] As such, all data presented in this submission and used in the updated cost-effectiveness model use the IRRC secondary definition of PFS.

Separation of the KM curves in Figure 3 (60-month data cut) occurs in favour of patients treated with NIVO+IPI after approximately 6 months from randomization (see Table 7 for PFS rates by treatment arm). After this timepoint, NIVO+IPI has consistently longer PFS than patients treated with sunitinib across the observed study period with an increasing incremental gain versus sunitinib in landmark PFS rates observed with additional follow-up. As seen in the KM curve and change in landmark PFS rates, a plateau appears to be forming [redacted] for NIVO+IPI, which is not observed for sunitinib. Of the patients who were progression-free at 2 years, [redacted] remained progression-free at 5 years with NIVO+IPI than with sunitinib [redacted] versus [redacted] respectively).

Consistent with the earlier 18-month data cut used for decision making in the original submission, the 60-month data shows patients treated with NIVO+IPI continue to demonstrate improvement in PFS compared with patients treated with sunitinib. Moreover, the HR (see Table 8) has improved from the 18-month data cut ([redacted]) to the 60-month data-cut ([redacted]). Patients treated with NIVO+IPI had a longer median PFS ([redacted]) compared with sunitinib ([redacted]). The 5-year PFS probability was greater with NIVO+IPI when compared with SUN ([redacted] versus [redacted] and of patients who remained alive at 5 years in either arm, [redacted] were



progression-free with NIVO+IPI versus [redacted] with sunitinib, further supporting the unique durable response seen with NIVO+IPI. It is clear from the KM curves and the [redacted] that NIVO+IPI offers significant and clinically relevant benefit for patients in terms of PFS versus sunitinib, which is sustained with longer term follow-up.

**Figure 3: KM curve of PFS IRRC secondary definition by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

**Key:** IRRC, independent radiology review committee; KM, Kaplan–Meier; PFS, progression-free survival.

**Table 7: Progression-free survival IRRC secondary definition rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

| Timepoint in months | Progression free survival rates by treatment, % | |
|---|---|---|
| | NIVO+IPI | Sunitinib |
| 1 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] |
| 24 | [redacted] | [redacted] |
| 36 | [redacted] | [redacted] |
| 48 | [redacted] | [redacted] |
| 60 | [redacted] | [redacted] |

**Key:** IRRC, independent radiology review committee.



**Table 8: Summary statistics for progression-free survival IRRC secondary definition by treatment arm – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

| Data cut | Treatment | n | Events | Censors | Median (m; 95% CI) | HR (CI)[a] |
|---|---|---|---|---|---|---|
| 18-m | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |
| | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |
| 60-m | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |
| | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** CI, confidence interval, HR, hazard ratio; m, months; n, number.
**Notes:** [a] Hazard ratio estimated from stratified Cox proportional hazards model. A hazard ratio of less than 1 favours NIVO+IPI; a hazard ratio greater than 1 favours sunitinib.

### *A.6.1.4 Time to treatment discontinuation*

TTD data using the 60-month data cut from CheckMate 214 were derived using the same method used in the original submission (TTD being defined as the time from first dose to when patient stops the randomized treatment; censoring patients if they remained on their randomized treatment at end of follow-up).

Figure 4 presents the KM curve and Table 10 presents summary statistics for TTD in the CheckMate 214 study by treatment arm (30-month and 60-month data cut). The KM curve shows that patients treated with NIVO+IPI and sunitinib have similar TTD until the curves cross and the treatments begin to separate [redacted] (see Table 9 for TTD rates by treatment arm). At this point, patients treated with NIVO+IPI have longer TTD than patients treated with sunitinib across the observed study period. This is also reflected in the summary statistics from the 60-month data cut; where median TTD is [redacted] for patients treated with NIVO+IPI and [redacted] for patients treated with sunitinib. Given the maturity of the TTD at the time of the



Final Appraisal Document (FAD), the relationship between NIVO+IPI and sunitinib remains largely unchanged (Appendix, Figure 36). At 60-months, the proportion of patients in the NIVO+IPI or sunitinib arm who had not discontinued treatment were [redacted] and [redacted], respectively (Table 9). It is worth noting that, as reported in Section A.6.1.3, [redacted] and [redacted] of patients remain progression-free in the NIVO+IPI and sunitinib arms, respectively; therefore, [redacted] of patients who are progression-free in the NIVO+IPI arm still are receiving treatment, demonstrating the ongoing clinical benefit despite treatment discontinuation. This treatment-free interval is further evidenced by swimmer plots presented in the appendix showing the proportion of patients achieving ongoing response but remaining off treatment and without any subsequent therapy (Figure 37 and Figure 38). Of the patients who have a complete response as their best overall response, a greater proportion of NIVO+IPI patients are off treatment and have not received subsequent treatments compared sunitinib ([redacted] versus [redacted] for NIVO+IPI and sunitinib, respectively (Figure 37). For patients who achieved a partial response as their best overall response, a similar trend is observed, with [redacted] of NIVO+IPI patients off treatment and never having received subsequent therapy versus [redacted] of patients in the sunitinib arm. [redacted] of patients in the sunitinib arm who achieved a complete or partial response have received subsequent systemic therapy versus [redacted] of those who achieved a response in the NIVO+IPI arm. These results, combined with the treatment-free interval indicated in red in the figures (Figure 37 and Figure 38), demonstrate a greater durability of response with NIVO+IPI than sunitinib that remains after treatment cessation.



**Figure 4: KM curve of time to treatment discontinuation by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

**Key:** KM, Kaplan–Meier.

**Table 9: Time to treatment discontinuation rates by treatment a CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

| Timepoint in months | Patients remaining on treatment, % | |
|---|---|---|
| | NIVO+IPI | Sunitinib |
| 1 | | |
| 3 | | |
| 6 | | |
| 12 | | |
| 24 | | |
| 36 | | |
| 48 | | |
| 60 | | |



**Table 10: Summary statistics for time to treatment discontinuation by treatment arm – CheckMate 214 intermediate-/poor-risk patients (30- and 60-month data cut)**

| Data cut | Treatment | n | Events | Censors | Median (m; 95% CI) | HR (95% CI)[a] |
|---|---|---|---|---|---|---|
| 30-m | Sunitinib | 416 | [redacted] | [redacted] | [redacted] | Reference |
| | NIVO+IPI | 423 | [redacted] | [redacted] | [redacted] | [redacted] |
| 60-m | Sunitinib | 416 | [redacted] | [redacted] | [redacted] | [redacted] |
| | NIVO+IPI | 423 | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** CI, confidence interval; HR, hazard ratio; m, months; n, number; TTD, time to treatment discontinuation.
**Notes:** [a] Hazard ratio estimated from Cox proportional hazards model. A hazard ratio of less than 1 favours NIVO+IPI; a hazard ratio greater than 1 favours sunitinib.

### *A.6.1.5 Immunological effect*

As demonstrated in sections A.6.1.1 to A.6.1.4, further follow-up from the CheckMate 214 trial shows that a greater proportion of patients are continuing to benefit across all endpoints when treated with NIVO+IPI compared with sunitinib.

Importantly, amongst patients with OS of at least 5 years who achieve a complete response or partial response as their best overall response, [redacted] of NIVO+IPI patients are off treatment and have not received subsequent therapy versus [redacted] of patients in the sunitinib arm, as shown in the swimmer plots in Figure 53 and Figure 54. Within this group of patients alive at 5 years who achieved a response, [redacted] of sunitinib patients have received subsequent therapy compared with [redacted] of NIVO+IPI patients. In addition, of those patients alive at 5 years, median PFS [redacted] for patients who achieved a partial response (Figure 55), further supporting the unique durable response seen with this dual checkpoint inhibitor regimen.



Of patients who have OS of at least 5 years, [redacted] of patients are still progression-free in the NIVO+IPI arm compared with [redacted] in the sunitinib arm. It is clear that the durable response seen with NIVO+IPI has also resulted in the relative PFS benefit versus sunitinib improving over time.

In the original submission, the company explored the relationship between immunotherapeutic survival benefit for durable responders. The committee considered the company's 15% estimate to be implausible because fewer than 15% of people were still on treatment at the end of follow-up (Table 1). With additional follow-up, it was demonstrated above that [redacted] of patients remain on treatment yet [redacted] are progression-free ([redacted]), further demonstrating a treatment-free interval and a unique immunotherapeutic effect observed with dual IO therapy.

Although a relationship between response and OS is not explicitly examined in the updated cost-effectiveness model for reappraisal, the 60-month evidence from CheckMate 214 demonstrates that there is a subset of patients treated with NIVO+IPI who continue to derive long-term benefit from NIVO+IPI, which is greater than in the sunitinib arm. Clinical validation expects these long-lasting responses from a proportion of patients treated with NIVO+IPI to result in mortality equivalent to that of the general population[7], and thus this has been considered in the choice of survival curve extrapolations for the cost-effectiveness model in Section A.7.3.

#### *A.6.1.6 Subsequent treatment*

The update of subsequent treatments from CheckMate 214 (60-month data cut) were derived using the same criteria used in the original submission, including systemic therapies received by 5% or more patients in either arm at any time during the trial. And as such, patients may have received and been recorded as having more than one type of subsequent therapy.

Table 11 presents the subsequent systemic treatment from CheckMate 214 from both the 60-month and 30-month data cut from the original submission. As expected with increased follow-up, subsequent treatment frequencies are higher than the original submission, with [redacted] of NIVO+IPI and [redacted] of sunitinib patients



receiving systemic subsequent treatment in the 60-month data cut. This data continues to demonstrate that more patients in the sunitinib arm receive subsequent systemic therapy than the NIVO+IPI arm over the same timeframe. In addition, of those systemic therapies, the most frequently received subsequent treatments are sunitinib after NIVO+IPI and nivolumab after sunitinib, representing [redacted] received, respectively. This evidence reinforces the long-term benefit of NIVO+IPI in the first-line setting, as there is not only a lower proportion of patients who require subsequent treatment, but there is also a greater proportion of patients who have discontinued therapy, but have not progressed and are not receiving second line treatment for RCC.

**Table 11: Subsequent treatment split by treatment arm from CheckMate 214 (5% or more patients in either arm, 30-month and 60-month data)**

| Subsequent treatment | CheckMate 214 30-month data | | | | CheckMate 214 60-month data | | | |
|---|---|---|---|---|---|---|---|---|
| | Nivolumab + ipilimumab (N = 425) | | Sunitinib (N = 422) | | Nivolumab + ipilimumab (N = 425) | | Sunitinib (N = 422) | |
| | n | % | n | % | n | % | n | % |
| No subsequent systemic treatment | [redacted] | | | | | | | |
| Patients who received systemic subsequent treatment | [redacted] | | | | | | | |
| Sunitinib | [redacted] | | | | | | | |
| Axitinib | [redacted] | | | | | | | |
| Pazopanib | [redacted] | | | | | | | |
| Cabozantinib | [redacted] | | | | | | | |
| Everolimus | [redacted] | | | | | | | |
| Nivolumab | [redacted] | | | | | | | |
| Lenvatinib | [redacted] | | | | | | | |
| Investigational antineoplastic* | [redacted] | | | | | | | |

**Notes:** * Although these are received by > 5% of patients in the 60-month data, these are not considered in cost calculations within the cost-effectiveness model, due to the uncertainty in drug price.
**, IRRC progression data were not updated in the 30-month datacut.



### *A.6.1.7 Quality of life*

As per the original appraisal, health state utilities were derived from statistical analysis of the EQ-5D-3L data for intermediate-/poor-risk patients in CheckMate 214 (60-month data cut) using the UK valuation tariff, in line with the National Institute for Health and Care Excellence (NICE) reference case, using a stepwise mixed-effects model. The utilities model included EQ-5D-3L as a function of progression, treatment arm and treatment status (on/off), using subject as a random effect to account for repeated measures. The step-wise approach begins with a model containing only the intercept with each subsequent model adding a main effect and associated interaction term with the model with the lowest Akaike information criterion (AIC) score being retained as the best-fitting. Results from this stepwise selection process are presented in A.15.5. The selected model (Model 7) captures treatment arm, progression status and treatment status (which was also used preferred by the ERG and NICE committee in the original submission). The resulting health state utilities calculated using this model, compared to those used in the CDF entry model are presented in Table 12.

**Table 12: Health state utility values from CheckMate 214 intermediate-/poor-risk patients EQ-5D-3L data**

| Economic model health states | 30-month | | 60-month | |
|---|---|---|---|---|
| | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |
| PFS On Tx, PPS On Tx* | 0.793 | 0.754 | [redacted] | [redacted] |
| PFS Off Tx | 0.749 | 0.707 | [redacted] | [redacted] |
| PPS Off Tx | 0.702 | 0.707 | [redacted] | [redacted] |

**Key**: EQ-5D-3L, EQ-5D 3-Level questionnaire; NIVO+IPI, nivolumab + ipilimumab; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.
**Note:** * Assumed equal as per ERG preference for CDF entry model.

Updated 60-month analyses of CheckMate 214 utility data are [redacted] to those from the 30-month analyses used in the CDF entry cost-effectiveness model (original appraisal). [redacted] important predictors of utility, and NIVO+IPI [redacted] in quality of



life for patients regardless of health state or treatment status when compared with sunitinib, with the greatest difference seen for patients who are [redacted]. Considering the relative maturity of PFS and TTD outcomes in the 30-month data, it is [redacted]. The 60-month off-treatment health states show [redacted] in utility across both arms for off-treatment progression-free patients, and off-treatment progressed patients have [redacted] utility in the 60-month data when compared with the 30-month for sunitinib patients, but the utility for NIVO+IPI patients has [redacted].

[redacted] with the results in the original appraisal, NIVO+IPI patients have a health-related quality of life benefit compared with sunitinib, that is [redacted].

### A.6.2 Systemic Anti-Cancer Therapy dataset

#### *A.6.2.1 Systemic Anti-Cancer Therapy patient cohort*

Between 5 April 2019 and 30 November 2020, a total of 814 patients were included in the systemic anti-cancer therapy (SACT) cohort and followed for a median 10.8 months (minimum and maximum follow-up of 5 and 24.7 months, respectively), which is considerably shorter than follow-up in CheckMate 214 assessed at CDF entry (30 months minimum). A summary of patient characteristics included in the SACT cohort is presented in the Appendix (Section A.15.1) alongside the NIVO+IPI CheckMate 214 population.

On the proportion of patients with poor-risk disease, there is a larger proportion of poor-risk patients in the SACT cohort (35%) compared to the CheckMate 214 cohort (21.4%) and at the clinical validation interview, both clinicians considered the SACT data to be more representative of their clinical practice than CheckMate 214.[1, 7] Specifically on the period of data collection, the characteristics of patients included in SACT are likely to have been impacted by COVID-19 (see Appendix Section A.15.9). A real-world study in the North West of England found the proportion of patients with poor-risk disease to be 28%.[8] These data suggest that there may be slightly more patients with poor-risk disease in UK clinical practice than CheckMate 214; however,



this is lower than that seen with the SACT data. In addition, CheckMate 214 included a higher proportion of poor risk patients (21% for NIVO+IPI) compared to KEYNOTE-426 (pembrolizumab plus axitinib versus sunitinib; 19% and 17% for pembrolizumab with axitinib and sunitinib, respectively) and a similar proportion compared to JAVELIN Renal 101 (avelumab plus axitinib versus sunitinib; 21% and 20% for avelumab plus axitinib and sunitinib, respectively) randomised controlled trials[9, 10], but the issue of the proportion of patients with poor-risk disease was not considered an area of uncertainty in the corresponding technical appraisals.[11, 12] As such, and considering the timing of data collection in relation to the COVID pandemic, it is considered inappropriate to use SACT data to inform the proportion of patients with intermediate-/poor-risk disease in this reappraisal.

### *A.6.2.2 Subsequent treatment*

The difference in follow-up of the SACT cohort compared with the CheckMate 214 data makes comparisons of subsequent treatment proportions between the two challenging. In the SACT cohort, 239/814 (29.4%) of patients who received NIVO+IPI went on to receive subsequent therapies after their last dose of NIVO+IPI was recorded in the SACT dataset. The most frequent subsequent treatment in the SACT cohort was cabozantinib whereas sunitinib was the most frequent subsequent treatment in CheckMate 214 NIVO+IPI patients.

**Table 13: Distribution of subsequent treatment SACT cohort (minimum follow-up: 5 months) and CheckMate 214 intermediate-/poor-risk patients (60-month minimum data cut)**

| Subsequent treatment | NIVO+IPI SACT (N = 814) | | NIVO+IPI CheckMate 214 (N = 425) | |
|---|---|---|---|---|
| | n | % | n | % |
| Proportion of patients receiving any subsequent systemic therapy | 239 | 29.4 | [redacted] | [redacted] |
| Cabozantinib | 145 | 17.8 | [redacted] | [redacted] |
| Sunitinib | 36 | 4.4 | [redacted] | [redacted] |
| Pazopanib | 29 | 3.6 | [redacted] | [redacted] |
| Tivozanib | 20 | 2.5 | [redacted] | [redacted] |
| Axitinib | 9 | 1.1 | [redacted] | [redacted] |
| Everolimus + lenvatinib | 18 | 2.2 | [redacted] | [redacted] |



| Subsequent treatment | NIVO+IPI SACT (N = 814) | | NIVO+IPI CheckMate 214 (N = 425) | |
|---|---|---|---|---|
| | n | % | n | % |
| Proportion of patients receiving any subsequent systemic therapy | 239 | 29.4 | [redacted] | [redacted] |
| Dabrafenib + trametinib | 2 | 0.2 | [redacted] | [redacted] |
| Carboplatin + pemetrexed | 1 | 0.1 | [redacted] | [redacted] |
| Everolimus | 3 | 0.4 | [redacted] | [redacted] |
| Irinotecan + mdg + panitumumab | 1 | 0.1 | [redacted] | [redacted] |
| Trial | 1 | 0.1 | [redacted] | [redacted] |
| Lenvatinib | 1 | 0.1 | [redacted] | [redacted] |
| Oxaliplatin + mdg + panitumumab | 1 | 0.1 | [redacted] | [redacted] |
| Nivolumab | NA | NA | [redacted] | [redacted] |
| Investigational antineoplastic | NA | NA | [redacted] | [redacted] |

**Note:** Some patients will have received more than one subsequent therapy. This table lists all subsequent therapies including those prescribed immediately.

# A.7 Incorporating collected data into the model

## A.7.1 Endpoints included in the analysis

To support the updated cost-effectiveness model and reduce uncertainty from the original appraisal, the following endpoints were re-analysed and included in the cost-effectiveness model:

- OS (CheckMate 214 60-month data)
- PFS per IRRC, secondary definition (CheckMate 214 60-month data)
- Time to treatment discontinuation (CheckMate 214 60-month data)
- Subsequent therapies (CheckMate 214 60-month data [base case] and SACT [scenario analysis])
- Health state utilities (CheckMate 214 60-month data)

## A.7.2 Analysis methodology

Parametric distributions were estimated for each endpoint as described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[13] Namely the following parametric curves were fitted: exponential, gamma, Weibull, Gompertz, log-



normal, log-logistic, and generalised gamma. Both independent and treatment effect models were considered.

Flexible parametric models (FPMs) were also considered in instances where the standard parametric models were unable to adequately capture the underlying shape of hazard functions.[14] This is the case for both PFS and TTD which have hazard functions with complex shapes, and thus FPMs were fitted using restricted cubic splines to enable the more complex hazards to be accurately modelled in line with NICE TSD 21.

There was uncertainty around the appropriateness of the proportional hazards (PH) assumption due to crossing of the log-cumulative hazard plots for PFS, OS and TTD and evaluation of the Schoenfeld residual plots (see Appendices A.15.2, A.15.3, and A.15.4 for further details) independent models are the preferred base case, which is also consistent with the original submission. NICE TSD 14 also states that 'when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach'.

Piecewise models, using the KM data, followed by an exponential curve from the point where the cumulative hazard plots show a constant hazard rate (as considered by the ERG and committee in the FAD[6]), were not considered here, due to the poor predictive performance of these extrapolations versus the 60-month CheckMate 214 data across both treatment arms (Figure 5). The extrapolated portion of these models consistently underestimates OS, and therefore the KM + exponential piecewise models were considered inappropriate for extrapolation in this setting. It is also apparent from Figure 5 that the company submitted base case curves also underpredicted the 5-year trial data and were conservative relative to the updated data.



**Figure 5: OS extrapolations based on 30-month CheckMate 214 (KM + exponential, log-logistic, and log-normal) versus OS 60-month CheckMate 214 KM data – intermediate-/poor-risk patients**

**Key:** DBL, database lock; EXP, exponential; KM, Kaplan-Meier.

### A.7.3 Results – OS

The smoothed hazard plots for the OS endpoint and fitted parametric survival models (Figure 19 and Figure 20, respectively) were used to assess the suitability of flexible parametric models. Many standard hazard functions for the parametric models provide a good visual fit to the data. The smoothed hazard function for the NIVO+IPI arm appears to increase rapidly following the 60-month timepoint where there is considerably more uncertainty in the tails of the hazard plot due heavy censoring after this time, requiring the use of a 12-month smoothing interval. Therefore, flexible parametric models were not considered necessary to sufficiently model OS data for the 60-month data cut; instead, the parsimony of standard parametric models were preferred.

The goodness-of-fit statistics (Appendix, Table 19) indicates that the log-normal extrapolation provides the best statistical fit to the data, as it has the lowest AIC and Bayesian information criterion (BIC) values when looking across both arms. The next best fitting curve (across both arms), generalised gamma, is fourth best fitting in



terms of BIC for NIVO+IPI and has a BIC difference from the lowest curve (log-normal) exceeding 5 points and a difference in 8.7 points in BIC across both arms. Other curves had even higher increases in AIC and BIC versus log-normal. When looking at the extrapolated period for each survival curve, the Gompertz, log-normal, and generalised gamma curves produced the highest survival estimates for the NIVO+IPI arm (Table 20). For the sunitinib arm, Gompertz and generalized gamma curves produced the most optimistic estimates. It should be noted that Gompertz is ranked fourth out of the seven models fitted and has a difference in AIC/BIC of over 20 points versus log-normal. All fitted curves are presented in Appendix Figure 21 for the NIVO+IPI and sunitinib arms.

During clinical validation interviews, clinicians were presented with log-normal, Weibull and exponential curves, as a range of representative extrapolations that also included the best (log-normal) and poor statistical fits (exponential and Weibull) according to AIC/BIC. Clinicians commented that for patients alive at 10 years, they would expect the impact of disease to be gone, and any survival events after this would be the same as those experienced by the general population. In addition, both clinicians expected the probability of death for patients surviving each year to decrease over time. Although clinicians found Weibull to best represent the expected survival at key timepoints in UK clinical practice, investigating the AIC/BIC (an increase of 45.7 points versus the best fitting curve; Appendix, Table 19), the hazard plots (Figure 19 and Figure 20, respectively), and extrapolations versus the KM data, as per NICE TSD DSU 14[13] and 21[14] recommendations, the Weibull model would not be appropriate to model CheckMate 214 observed data for either treatment arm. As such, log-normal (as the best fit statistically, with function able to reflect long-term hazard expectations) were considered the best choice for base case curves on both arms, with their intrinsic immunological effect assumptions investigated further within the cost-effectiveness model (A.7.3.1).

#### *A.7.3.1 Immunological effect*

As discussed in Section A.6.1.5, additional CheckMate 214 follow-up demonstrates the continued durable responses from NIVO+IPI that are not observed with sunitinib, with more than half of responses still ongoing at 60 months in the NIVO+IPI arm. In



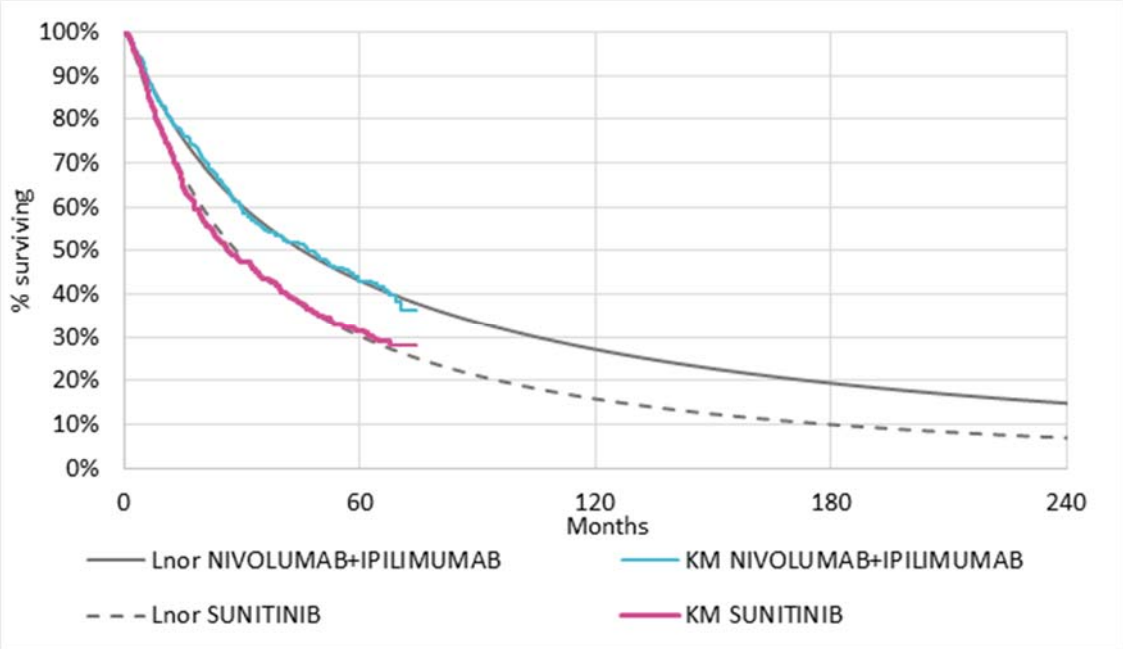
 

addition, [redacted] of patients who received NIVO+IPI and achieved a complete or partial response have discontinued first-line therapy and never received any subsequent systemic therapy. However, a response-based long-term survivorship effect is not explicitly modelled in OS considerations for the cost-effectiveness model. The proportion of patients reaching general population mortality was explored to ensure alignment with clinical expectation. Interviewed clinicians expressed an expectation of patients reaching general population mortality at around 10 years. In addition, they considered that 10–15% of patients would not have disease progression before death.[7] When considering a log-normal extrapolation (the extrapolation with the best statistical fit across both arms and a hazard function representative of clinical expectation), 15.9% of NIVO+IPI patients and 6.2% of sunitinib patients reach this mortality rate and cap at 19 and 21 years, respectively. The probability of remaining alive for an additional two years has increased from 66% (at study start) to 79% (at year 3) for patients in the NIVO+IPI arm, and conditional OS is consistently higher for NIVO+IPI than sunitinib (two-year conditional OS from 3 year landmark: 79% versus 72%, respectively), which is in line with clinical expectations of a decreasing probability of death over time. As such, a log-normal (Figure 6) extrapolation is justified in respect to clinical expectation of a long-term survivorship and is considered the base case curve for OS extrapolation. This base case curve selection is consistent with the original submission when the 30-month data cut was used, which was shown in Figure 5 to have [redacted] the 60-month minimum follow-up data used in this submission.



**Figure 6: OS extrapolations log-normal – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**




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

### *A.7.3.2 Treatment switching*

[redacted] randomized to sunitinib crossed over to NIVO+IPI. As this is only a small proportion of patients, and due to the likelihood of any given sunitinib patient receiving subsequent nivolumab, it was considered that the impact of adjusting for this crossover would be minimal. Although not adjusting for crossover is a conservative assumption, biasing against NIVO+IPI, the addition of such analyses would add additional complexity and uncertainty to the cost-effectiveness model and results, with limited additional information. As such, no crossover analyses have been presented for this reappraisal, as agreed at the NICE CDF review kick-off meeting.

## A.7.4 Results – progression-free survival per IRRC (secondary definition)

Visual assessment of the smoothed hazard plots for the PFS endpoint and fitted hazard functions of the standard parametric survival models (Figure 28 and Figure



29) show that the standard parametric models do not adequately capture the shape of the hazard functions. The hazard function presented in Appendix Figure 28 appears to provide a good visual fit to the smoothed hazard in the NIVO+IPI arm. However, for the sunitinib arm (Figure 29) the hazard is poorly modelled by the standard parametric survival models with the smoothed hazard displaying a constant hazard from approximately the 24-month timepoint. Therefore, flexible parametric models were explored to provide a better fit to the observed data.

The goodness-of-fit statistics (Appendix, Table 21) indicate that the hazard spline two-knot provides the best statistical fit to the data for both arms, as it has the lowest AIC and BIC values further supporting the notion that standard parametric models did not provide a particularly good fit to the data both visually and statistically. Of the flexible parametric models with two-knots, the odds and normal splines consist of the most optimistic extrapolations, with the hazards spline representing the most conservative estimates.

The hazard spline 2-knot curve (Figure 7 and Figure 8) provided the best visual and statistical fit to the data and was therefore selected as the base case for the economic model for both treatment arms. This is consistent with the original submission when the 30-month data cut was used as cubic splines were preferred (spline 2-knot hazard to NIVO+IPI and a spline 1-knot hazard model fit to sunitinib arm). Clinical validation also confirmed that spline 2-knots hazard was reflective of clinical practice, with some in the clinical community expecting even better results than these models predicted for NIVO+IPI. Interviewed clinicians expected the PFS curve to eventually meet the OS curve, with potentially 10–15% of patients expected not to have any disease progression before death.[7] The fitted curves for the alternative 1-knot models are presented in Figure 32 and Figure 33 for the NIVO+IPI and sunitinib arms, respectively.



**Figure 7: PFS per IRRC (secondary definition) extrapolations splines NIVO+IPI 2-knot – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**

**Key:** IRRC, independent radiology review committee; PFS, progression-free survival.

**Figure 8: PFS per IRRC (secondary definition) extrapolations splines sunitinib 2-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Key:** IRRC, independent radiology review committee; PFS, progression-free survival.

### A.7.5 Results – time to discontinuation

Visual assessment of the smoothed hazard plots for the TTD endpoint with the fitted hazard functions of the parametric survival models presented in TSD 14 (Appendix



Figure 42 and Figure 43) show that the standard parametric models may not adequately capture the shape of the hazard functions. Spline models were explored to capture the complexity in the hazard function that parametric survival models may not adequately model for TTD; these are presented in Figure 44 to Figure 47. The model fit statistics are presented in Table 22. The goodness-of-fit statistics indicated that a number of the models provided similar statistical fit for both treatment arms based on the AIC and BIC values (many models were within 5 of the best fitting model). The fitted curves are presented in Figure 48 to Figure 52 for the NIVO+IPI and sunitinib arms.

However, previous clinical validation collected during the initial appraisal found that clinicians would consider treatment discontinuation for long-term responders when cumulative toxicity is considered to tip the balance of risk–benefit ratio of ongoing therapy.[15] [redacted].[6] Further clinical validation in preparation for this CDF review found that clinicians would be sceptical that any patients in clinical practice would remain on treatment for 5 years, given NIVO+IPI's mechanism of action, and stopping rules seen in other indications. In clinical practice, a small number of patients have chosen to discontinue treatment at 2–3 years after discussion with their clinician. Both clinicians commented on the challenge of these discussions, as there are little data to base these decisions on, and most patients would want to continue. However, given all this, both clinicians found [redacted] to be reflective of their expectations, if not a little optimistic.[7]

For sunitinib, clinicians thought a small number of patients (approximately 2%) would still be on treatment at 5 years, but none at 10 years of which the [redacted] models match these estimates. [redacted] Given the consistent clinical feedback on the expected duration of NIVO+IPI treatment over time across both appraisals, [redacted]



### A.7.6 Subsequent treatment

The proportion of patients receiving subsequent treatments, and the proportion of each subsequent treatment received were updated in the cost-effectiveness model using the 60-month CheckMate 214 data for the base case (Table 11, excluding investigational antineoplastic), and a new scenario analysis using the treatment proportions taken from SACT (those received by more than 5% patients receiving any subsequent therapy) was included.

During validation interviews, clinicians found the 60% and 80% of patients receiving subsequent treatment at progression after NIVO+IPI and sunitinib, respectively to be overly optimistic. Both clinicians considered a 50% subsequent treatment rate across both arms to be expected in UK clinical practice. The difference between the two arms is expected to be small, due to a high proportion of sunitinib patients being too ill to receive subsequent treatment, and a high proportion of NIVO+IPI patients still receiving long-term clinical benefit from NIVO+IPI as to not require any subsequent treatment (see swimmer plots for complete and partial responders in Appendix Figure 37 and Figure 38, respectively).[7] As such, the updated CheckMate 214 (60-month) data on the proportion of patients receiving any subsequent therapy (Table 11) is used to inform the proportion of patients who are off first-line treatment and alive receiving subsequent therapy in the base case. This allows the proportions used to reflect the expectations of clinicians more accurately, whilst also demonstrating the difference in subsequent treatment rate seen in CheckMate 214. In addition, the distribution of each subsequent treatment received is taken from CheckMate 214 in the base case in order to align modelled efficacy and costs, as per the preference of the ERG and committee in the original submission.

The SACT subsequent therapy data forms an exploratory alternative scenario for the distribution of each treatment received. It is worth noting that such a scenario should be viewed as purely assessing variability on costs as it is not possible to reflect any differences in terms of outcomes, which would be affected by differences in subsequent treatment. Therefore, this scenario should not be considered for decision making, as it does not align with actual OS from the CheckMate 214 trial. This exploratory scenario considers both the first and further subsequent treatments



recorded in SACT after treatment with NIVO+IPI. In the absence of SACT subsequent treatment data after first line treatment of sunitinib and pazopanib, patients are assumed to receive 60% nivolumab (in line with previous NHS England estimates from the original appraisal[6]), with other subsequent treatments reweighted in the same proportion as those of the SACT NIVO+IPI patients (minus sunitinib and pazopanib, respectively). Commenting on the suitability of the distribution of treatments used as subsequent therapy in SACT, interviewed clinicians broadly thought that the data matched their expectations of clinical practice. In the centres of the two clinicians interviewed, their practice would be to use either cabozantinib or tivozanib post NIVO+IPI, depending on how quickly the patient was progressing. However, they acknowledged that pazopanib and sunitinib are still used in other centres. Following sunitinib (or pazopanib), these same tyrosine-kinase inhibitor choices and preferences would follow for some patients, but they would expect the majority of patients to receive nivolumab.[7]

As a simplifying assumption, the therapies that have met the threshold for inclusion in the cost-effectiveness model using the 60-month CheckMate 214 or SACT data (treatments received by more than 5% patients receiving any subsequent therapy) but were not included in the cost-effectiveness model used for CDF entry (lenvatinib and tivozanib) have been costed as similar priced therapies (axitinib and sunitinib, respectively). As these are only received by a small fraction of patients, the impact of this assumption is expected to be minimal.

### A.7.7 Quality of life

Table 12 presents the updated 60-month CheckMate 214 utility values applied in the model by health state.

## A.8 Key model assumptions and inputs

Analyses were conducted using the committee's preferred assumptions from the original appraisal but using the more mature CheckMate 214 data to revisit survival analyses, subsequent therapy proportions and their associated assumptions, and



updated utility data. Scenario analyses have been conducted to explore alternative subsequent therapy and time-to-event extrapolation assumptions (Section A.11).

Table 14 presents the key changes in the model inputs from the previous submission compared with the post-CDF submission.

**Table 14: Key model assumptions and inputs**

| Model input and cross reference | Original parameter /assumption | Updated parameter /assumption | Source/Justification |
|---|---|---|---|
| Overall survival extrapolation of sunitinib and NIVO+IPI (Section A.7.3) | Independent log-normal (Company) or KM+exp (ERG) extrapolation CheckMate 214 (30-month) | Independent log-normal parametric extrapolations from CheckMate 214 (60-month), unadjusted for crossover | Goodness of fit statistics, visual inspection, fit to observed data, and expectation of long-term survivorship for a subset of patients (aligned with clinical opinion) demonstrates that the log-normal is the best fitting extrapolation for the updated clinical data for both treatment arms<br>KM+exp extrapolations considered at CDF entry were judged as inappropriate due to the poor predictive performance with 60-month CheckMate 214 data (Figure 5), poor goodness of fit statistics and poor visual fit of the exponential hazard to hazards for either treatment arm<br>As agreed at the CDF review kick-off meeting with NICE, crossover analyses were deemed inappropriate and not included (Section A.7.3.2) |
| Progression-free survival extrapolation of sunitinib and NIVO+IPI (Section A.7.4) | KM+exp extrapolation CheckMate 214 (30-month) | Hazard spline model (2 knots) extrapolation from CheckMate 214 (60-month) | Data from the latest data cut from CheckMate 214 have been used for progression-free survival parametric extrapolation in the model. Goodness of fit statistics, visual inspection and clinical validation suggests that the hazard spline model (2 knots) is the best fitting extrapolation for the updated clinical data [redacted] observed emerging plateau |
| Time to treatment discontinuation of sunitinib and NIVO+IPI (Section A.7.5) | [redacted] | [redacted] | [redacted] |



| Model input and cross reference | Original parameter /assumption | Updated parameter /assumption | Source/Justification |
|---|---|---|---|
| | | | [redacted] |
| Proportion of patients with subsequent treatment and treatment distributions (A.6.1.5 and A.7.6) | CheckMate 214 (30-month) | CheckMate 214 (60-month; base case) and SACT data (exploratory scenario analysis) | CheckMate 214 (60-month) data were selected for the proportion of patients receiving subsequent therapy as the base case to reflect both clinical expectation and differences across arms in trial data<br>Subsequent treatment distributions were taken from updated CheckMate 214 data in the base case to align costs with outcomes. Real-world SACT data were considered as an exploratory scenario analysis. |
| Health-related quality of life (A.6.1.7 and A.7.7) | CheckMate 214 (30-month) | CheckMate 214 (60-month) | Updated stepwise regression analysis of CheckMate 214 data demonstrates treatment arm, treatment status and progression status remain important determinants of patients' utility. |

**Key:** CDF, Cancer Drugs Fund; ERG, evidence review group; KM, Kaplan–Meier; NICE, National Institute of Health and Care Excellence.

## A.9 Cost-effectiveness results (deterministic)

As discussed in Section A.7, the updated CheckMate 214 data has provided updated survival analyses for TTD, PFS and OS, along with updated subsequent therapy proportions in the base case. Further changes include updates to the confidential nivolumab patient access scheme (PAS) ([redacted]) and corrections in coding logic in the patient flow sheets.

The incremental cost-effectiveness ratio (ICER) for the updated company base-case is £25,827 versus sunitinib and £24,543 versus pazopanib. This demonstrates that NIVO+IPI remains cost-effective with the 60-month update of the CheckMate 214 data at a willingness-to-pay threshold of £30,000/quality-adjusted life year (QALY). At the time of CDF entry, three different OS extrapolations and their associated ICERs were considered potentially plausible (KM plus exponential, log-logistic and



log-normal). As the KM plus exponential model has now been shown to predict future survival poorly (Figure 5), and as log-normal is considered the best fitting curve for the updated CM214 data, the reference ICER for Table 15 is that from the cost-effectiveness model extrapolating OS for NIVO+IPI and sunitinib using an independent log-normal function. However, all decision making ICERs from the original submission can be replicated in the updated cost-effectiveness model.



**Table 15: Cost-effectiveness results (deterministic, PAS price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| **Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (log-normal for OS extrapolation, 30-month CM214 data)** | | | | | | | | |
| NIVO+IPI | [redacted] | 7.93 | 4.40 | | | | | |
| Sunitinib | [redacted] | 5.05 | 2.99 | £41,374.51 | 2.88 | 1.41 | – | £29,410.24 |
| Pazopanib | [redacted] | 5.05 | 2.99 | £39,449.48 | 2.88 | 1.41 | – | £28,041.88 |
| **Cost-effectiveness analysis 2: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (log-normal for OS extrapolation, 30-month CM214 data) with correction to resource use** | | | | | | | | |
| NIVO+IPI | [redacted] | 7.93 | 4.40 | | | | | |
| Sunitinib | [redacted] | 5.05 | 2.99 | £42,901.63 | 2.88 | 1.41 | +£1,014.44 | £30,424.68 |
| Pazopanib | [redacted] | 5.05 | 2.99 | £40,876.60 | 2.88 | 1.41 | +£1,014.44 | £29,056.31 |
| **Cost-effectiveness analysis 3: New company base-case (corrections from FAD model and updated PAS) with 60-month CM214 data** | | | | | | | | |
| NIVO+IPI | [redacted] | 8.08 | 4.62 | | | | | |
| Sunitinib | [redacted] | 5.35 | 3.13 | £38,451,47 | 2.73 | 1.49 | -£3,583.49 | £25,826.75 |
| Pazopanib | [redacted] | 5.35 | 3.13 | £36,539.85 | 2.73 | 1.49 | -£3,499.11 | £24,542.77 |

**Key:** CDF, Cancer Drugs Fund; FAD, Final Appraisal Document; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.



## A.10 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed for 1,000 iterations at which point the ICERs had stabilized. In each iteration, the model inputs were randomly drawn from the specified distributions, summarized in Table 24.

The mean probabilistic incremental costs and QALYs gained from NIVO+IPI with the PAS applied across the 1,000 iterations are given in Table 16. The deterministic and probabilistic outputs are similar, highlighting the robustness of the estimates. The visual results of the probabilistic sensitivity analysis runs are presented in Figure 9, Figure 10 and Figure 11. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option is 93.3% (Figure 9). This is considerably higher than at the time of the original company submission (~50%), and the cost-effectiveness clouds are also considerably smaller than those presented in the original company submission, driven by the reduced uncertainty in OS and TTD extrapolations and improved cost-effectiveness results.

**Figure 9: Cost-effectiveness acceptability curve – B.3.8.1 (page 150)**

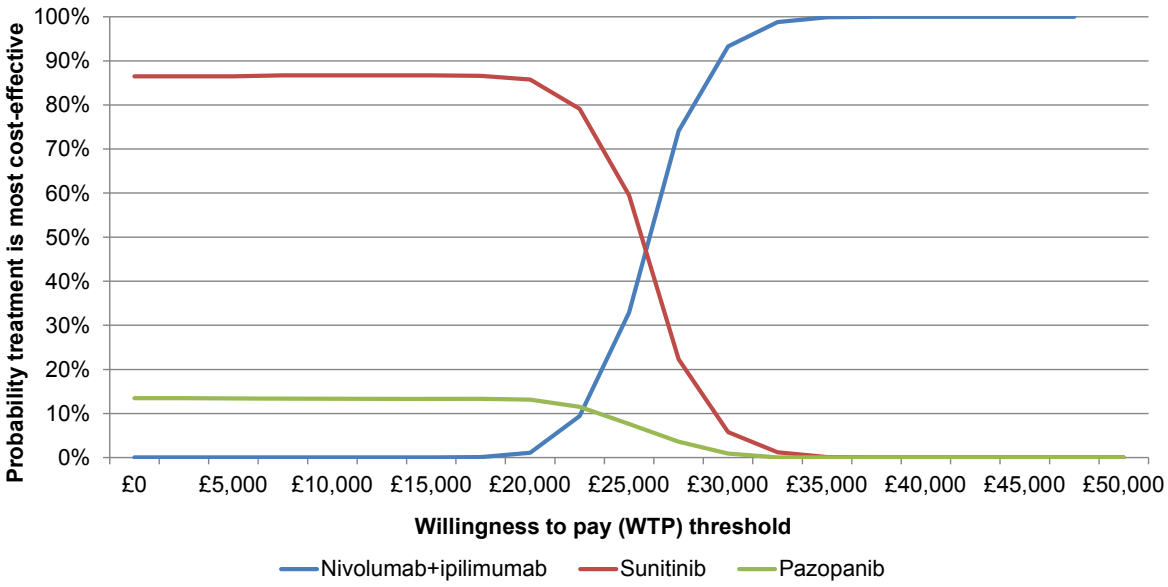




**Table 16: Updated base-case results (probabilistic) – B.3.8 (page 151)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus deterministic (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| NIVO+IPI | [redacted] | 8.09 | 4.61 | | | | | |
| Sunitinib | [redacted] | 5.35 | 3.13 | £38,490.08 | 2.74 | 1.49 | £70.32 | £25,897.07 |
| Pazopanib | [redacted] | 5.35 | 3.13 | £36,647.34 | 2.74 | 1.49 | £110.10 | £24,652.86 |
| **Key:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; NIVO+IPI, nivolumab plus ipilimumab; QALY, quality-adjusted life year. | | | | | | | | |



**Figure 10: PSA scatterplot, NIVO+IPI versus sunitinib – B.3.8.1 (page 149)**

**Key:** ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSA, patient access scheme; WTP, willingness to pay.

**Figure 11: PSA scatterplot, NIVO+IPI versus pazopanib – B.3.8.1 (page 150)**

**Key:** ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSA, patient access scheme; WTP, willingness to pay.



## A.11 Key sensitivity and scenario analyses

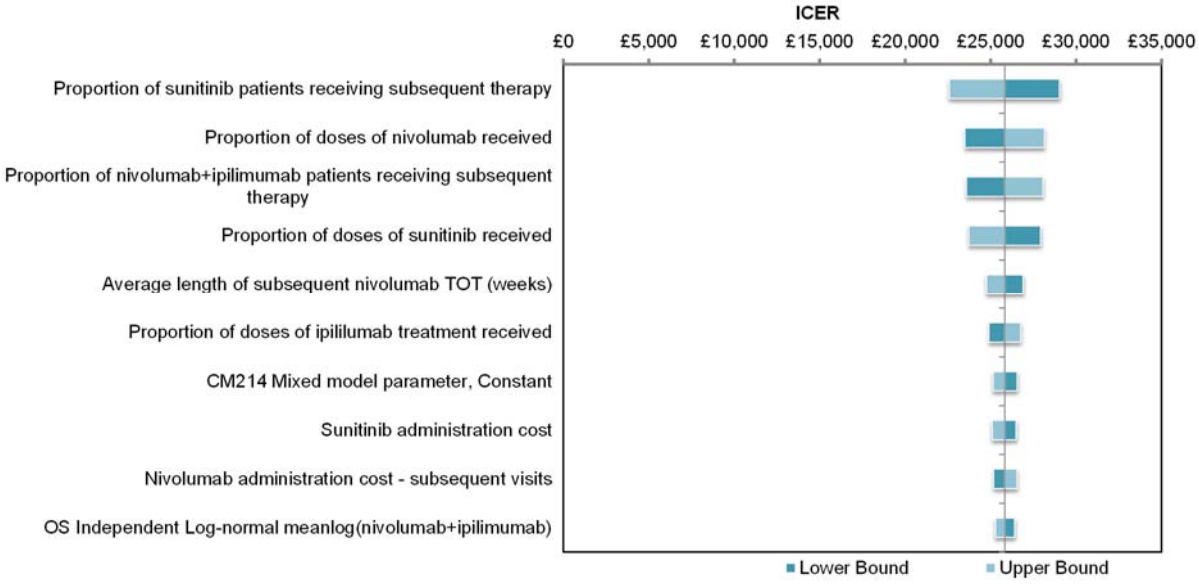
Figure 12 and Figure 13 present the top 10 drivers of cost-effectiveness with descending sensitivity from the one-way sensitivity analysis when nivolumab is provided with the PAS agreement versus sunitinib and pazopanib, respectively. The ICERs were most sensitive to parameters relating to those informing subsequent therapy proportions for both sunitinib and NIVO+IPI, followed by the proportion of doses received and administration costs. These are similar to those presented in the original company submission, but without parameters informing TTD and immuno-oncology effect. With greater follow-up, not only has the uncertainty decreased around the impact on the ICER (range between the upper and lower bound is reduced), but all drivers in the one-way sensitivity analysis (OWSA) are below the £30,000 per QALY threshold.

In the original submission, TTD parameters resulted in the greatest uncertainty in the OWSA. With greater follow-up, TTD parameters are no longer a top 10 driver and have less influence on overall model results as uncertainty is reduced due to greater follow-up from Checkmate 214. Immuno-oncology effect parameters no longer feature in the updated tornado as these inputs are set to zero in this updated cost-effectiveness model, as it is assumed the long-term survivorship benefit for NIVO+IPI and subsequent nivolumab is intrinsically captured within the log-normal OS extrapolation. As such, varying these immuno-oncology parameters does not have any effect on model results.



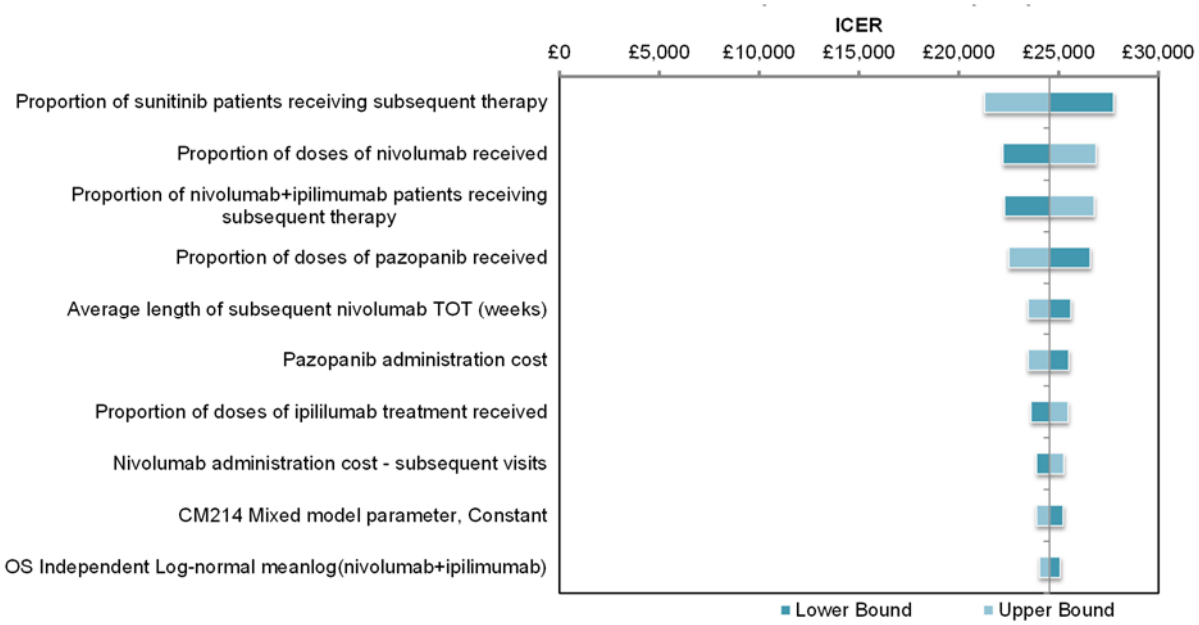
 

**Figure 12: Tornado diagram showing OWSA results, NIVO+IPI versus sunitinib**




**Key:** ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; TOT, time on treatment.

**Figure 13: Tornado diagram showing OWSA results, NIVO+IPI versus pazopanib**




**Key:** ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PSA, patient access scheme; WTP, willingness to pay.

Table 17 presents scenario analyses for each updated set of inputs in the cost-effectiveness model. OS remains one of the biggest drivers of cost-effectiveness, but



NIVO+IPI remains cost-effective when testing the use of alternative PFS and TTD model extrapolations and subsequent therapy inputs.

**Table 17: Key scenario analyses**

| Scenario and cross reference | Scenario detail | Brief rationale | Impact on base-case ICER | |
|---|---|---|---|---|
| | | | versus sunitinib | versus pazopanib |
| **Base case** | | | **£25,827** | **£24,543** |
| Log-normal parametric extrapolation CheckMate 214 (60-month) for OS | Generalised Gamma extrapolation CheckMate 214 (60-month) for OS | Alternative extrapolation with next best statistical fit | £29,432<br>+£3,605 | £27,946<br>+£3,403 |
| Hazard spline model (2 knots) extrapolation CheckMate 214 (60-month) for progression-free survival | Generalised gamma extrapolation CheckMate 214 (60-month) for progression-free survival (60-month) for OS | Clinically validated model | £25,353<br>-£474 | £24,079<br>-£463 |
| Fully-fitted [redacted] extrapolation CheckMate 214 (60-month) for time to treatment discontinuation | [redacted] CheckMate 214 (60-month) for time to treatment discontinuation | [redacted] was statistically the best fitting model | £27,396<br>+£1,569 | £26,077<br>+£1,534 |
| Subsequent therapy CheckMate 214 (60-month) | SACT subsequent therapy | Exploratory scenario to estimate costs based on limited real world data from NHS England clinical practice | £27,883<br>+£2,056 | £26,600<br>+£2,057 |

**Key:** ICER, incremental cost-effectiveness ratio; OS, overall survival, SACT, systemic anti-cancer therapy.

## A.12 End-of-life criteria

As per the final appraisal document (FAD) for TA581 and terms of engagement, the end-of-life criteria are not expected to be met for NIVO+IPI in this indication.



## A.13 Key issues and conclusions based on the data collected during the CDF review period

The updated 60-month follow-up for CheckMate 214 provides additional evidence of the continued long term clinical benefit for patients treated with NIVO+IPI versus those treated with sunitinib, providing greater confidence and certainty in the added benefit that NIVO+IPI brings to intermediate-/poor-risk patients with RCC to the NHS.

Revisiting survival analyses with a minimum follow-up of 60 months from CheckMate 214 has provided greater certainty in long-term survival extrapolations, and an insight into the performance of previous survival models considered by the ERG and committee. The 60-month OS data shows a greater benefit than that predicted by all models considered at CDF entry (log-normal, log-logistic and KM + exponential). (Figure 5). In addition, the longer-term follow up has demonstrated the appropriateness of survival models that consider decreasing hazards in the long term, especially as conditional survival has increased over time in the CheckMate 214 study.

Other outcome data from the CheckMate 214 60-month data cut continue to demonstrate the long-term benefit provided by NIVO+IPI, with long-lasting, durable responses, the possibility for a prolonged treatment-free interval for patients who respond to NIVO+IPI and maintained progression-free and overall survival benefits compared with sunitinib for those who respond. These data provide strong evidence for a proportion of patients who will go on to achieve long-term survival, as expected by clinicians. The relationship between treatment response, response duration and OS has not been directly modelled here, but the extrapolations presented within this reappraisal allow the consideration of some patients with long-term survivorship without explicitly modelling any type of immunotherapeutic effect.

As well as not explicitly modelling long-term survivorship, OS extrapolations here should also be considered conservative as no adjustment has been made for treatment switching. With [redacted] of sunitinib patients crossing over to NIVO+IPI in CheckMate 214, the current cost-effectiveness model is likely to overpredict survival



on the sunitinib and pazopanib arms, as well as underpredict the total costs associated with these patients crossing over.

Updated additional subsequent therapy data from CheckMate 214 remain similar to those presented in the original submission and have remained as the base case to align costs and benefits. However, an exploratory analysis has been provided based on SACT data collected, though BMS do not believe this scenario should be considered for decision making due to the limited follow-up available and timing of data collection. The model results are robust to alternative assumptions using the SACT data for subsequent treatments received after NIVO+IPI (and sunitinib), though it is important to note prescribing patterns may have been impacted by the COVID-19 pandemic.

In conclusion, the updated survival data collected during the CDF and updated cost-effectiveness model continue to show a strong clinical benefit for NIVO+IPI versus sunitinib and pazopanib, and that it remains cost-effective at a WTP threshold of £20,000 to £30,000, with considerably reduced uncertainty, and potentially conservative survival assumptions.



## A.14 References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# A.15 Appendices

## A.15.1 Summary of patient baseline characteristics – CheckMate214 and SACT cohort

**Table 18: CheckMate 214 patient characteristics versus Systemic Anti-Cancer Therapy data cohort**

| Patient characteristics | NIVO+IPI (CheckMate214 N = 425) | NIVO+IPI (SACT N = 814) |
|---|---|---|
| **Gender** | | |
| Male | 314 (73.9%) | 596 (73%) |
| Female | 111 (26.1%) | 218 (27%) |
| **Age** | | |
| <40 | 5 (1.2%) | 15 (2%) |
| 40-49 | 48 (11.3%) | 96 (12%) |
| 50-59 | 121 (28.5%) | 257 (32%) |
| 60-69 | 158 (37.2%) | 271 (33%) |
| 70-79 | 71 (16.7%) | 167 (21%) |
| 80+ | 8 (1.9%) | 8 (1%) |
| Exact age not recorded | 14 (3.3%) | NA (0%) |
| **Histology** | | |
| RCC with a clear cell component | 425 (100%) | 740 (91%) |
| Papillary RCC | 0 (0%) | 74 (9%) |
| **Previous treatment** | | |
| No previous adjuvant systemic therapy of any kind | 425 (100%) | 804 (99%) |
| Prior clinical trial with adjuvant therapy with immune-modulatory therapies | 0 (0%) | 5 (1%) |
| Prior clinical trial with adjuvant therapy with agents which target VEGF | 0 (0%) | 5 (1%) |
| **IMDC prognostic group** | | |
| Intermediate risk disease (IMDC score of 1 or 2) | 334 (78.6%) | 533 (65%) |
| Poor risk disease (IMDC score of 3-6) | 91 (21.4%) | 281 (35%) |
| **Key**: SACT, systemic anti-cancer therapy; RCC, renal cell carcinoma; IMDC, international metastatic database consortium. | | |



### A.15.2 OS – CheckMate 214

**Figure 14: CheckMate 214 OS by best overall response, 60-month follow-up, NIVO+IPI (left) and sunitinib (right)**



**Figure 15: KM curve of OS by treatment arm – CheckMate 214 intermediate/poor risk patients (30-month and 60-month data-cut)**

**Key:** DBL, database lock; KM, Kaplan-Meier; OS, overall survival.

### *A.15.2.1 Assessing proportional hazards and accelerated failure time*

An assumption of PH across the two treatment arms of CheckMate 214 was first evaluated to assess whether survival analysis stratified by treatment arm was appropriate. Figure 16 shows the log-cumulative hazard plot for OS in intermediate-/poor-risk patients in CheckMate 214. This log-cumulative hazard plot, alongside the KM curve (Figure 1) and the Schoenfeld residual plot (Appendix, Figure 17) were used to assess the plausibility of a PH assumption. Although the Schoenfeld test does not reject the PH assumption (p = 0.4554), the crossing of the log-cumulative hazards plots assumption may be violated when whole treatment period is considered. Therefore, models fitted to independent treatment arms are considered as the base case, supported by a clinical perspective from the original submission where 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 across the whole treatment period. (See TA581 Document B, Section B.3.3.1, Page 76).



**Figure 16: Log-cumulative hazard plot for OS – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

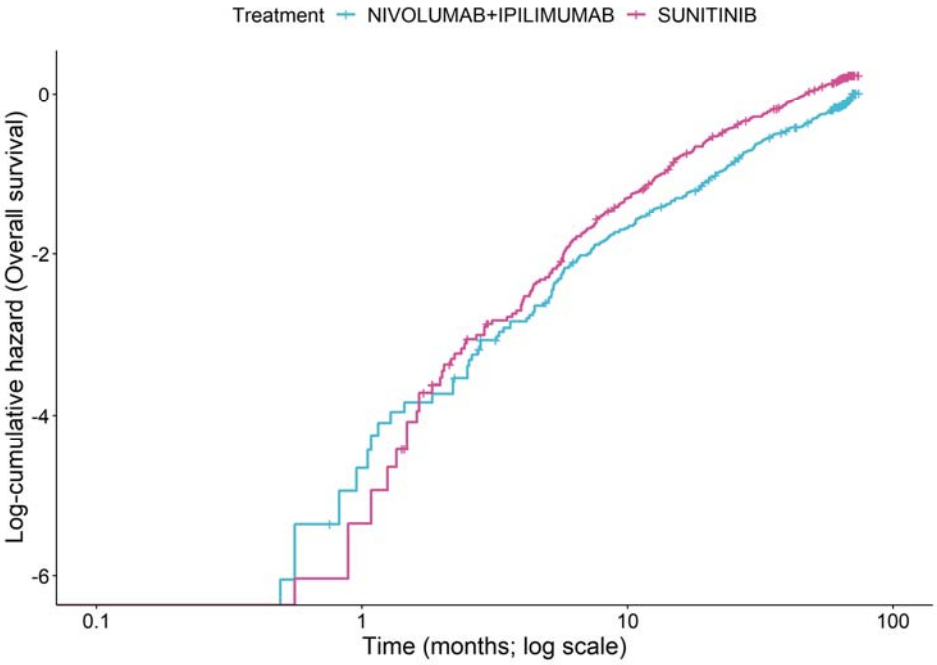
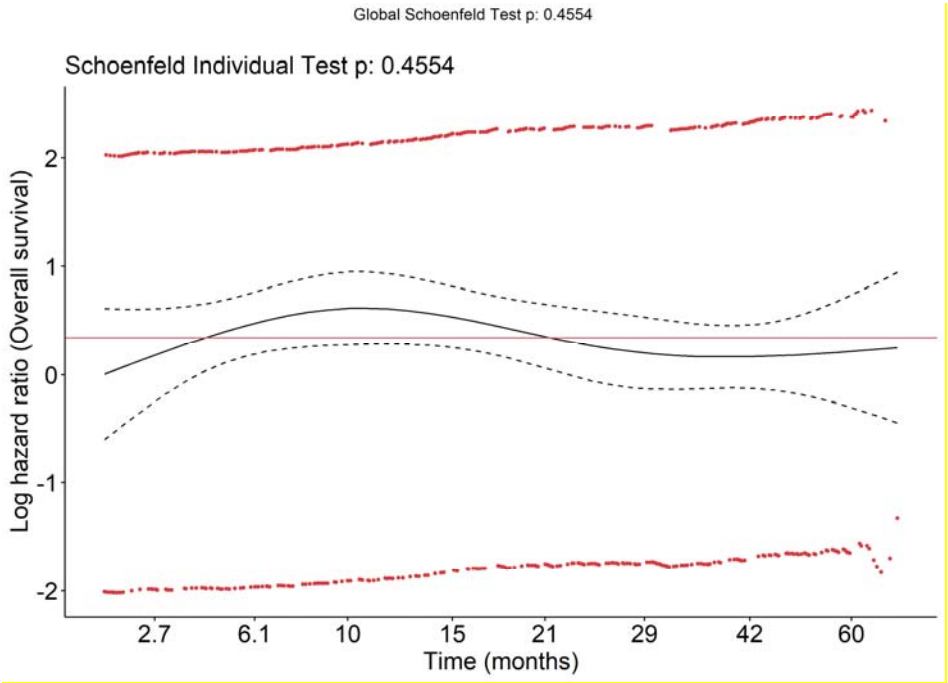



**Figure 17: Schoenfeld residual plot for OS – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

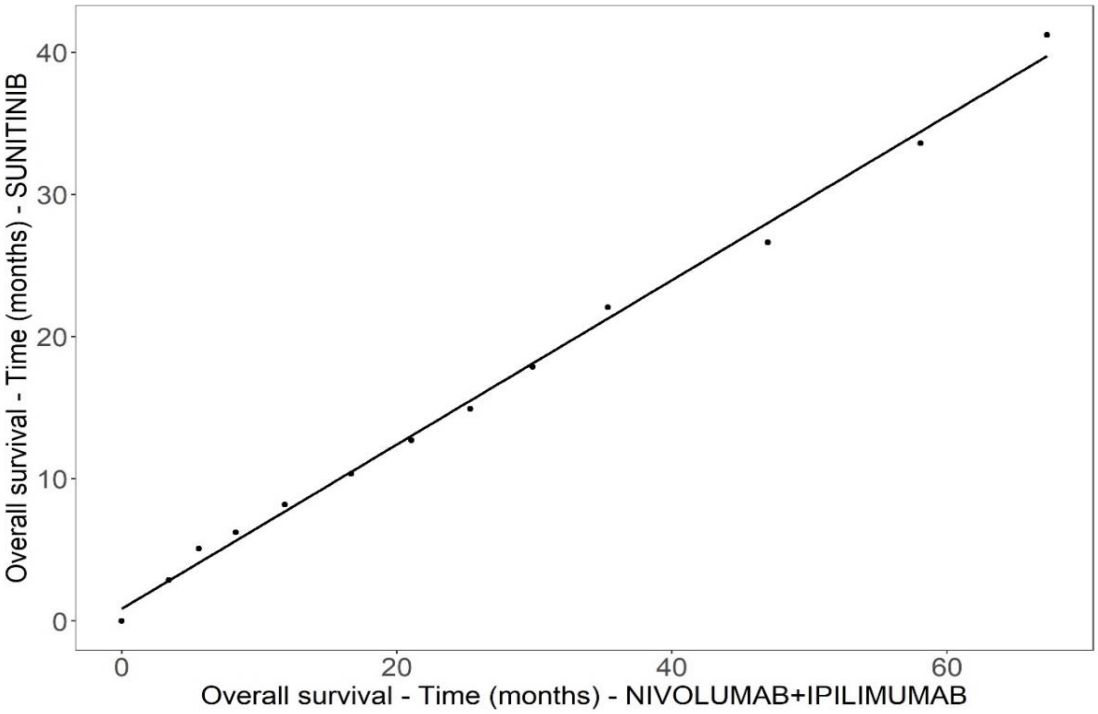




**Notes:** Red dots indicate Schoenfeld residuals; solid black line indicates time varying log hazard ratio; dashed black line indicates log-hazard ratio ± 2 standard errors; solid red line indicates constant log-hazard ratio.

## Figure 18: Quantile-quantile plot for OS – CheckMate 214 intermediate/poor risk patients (60-month data cut)

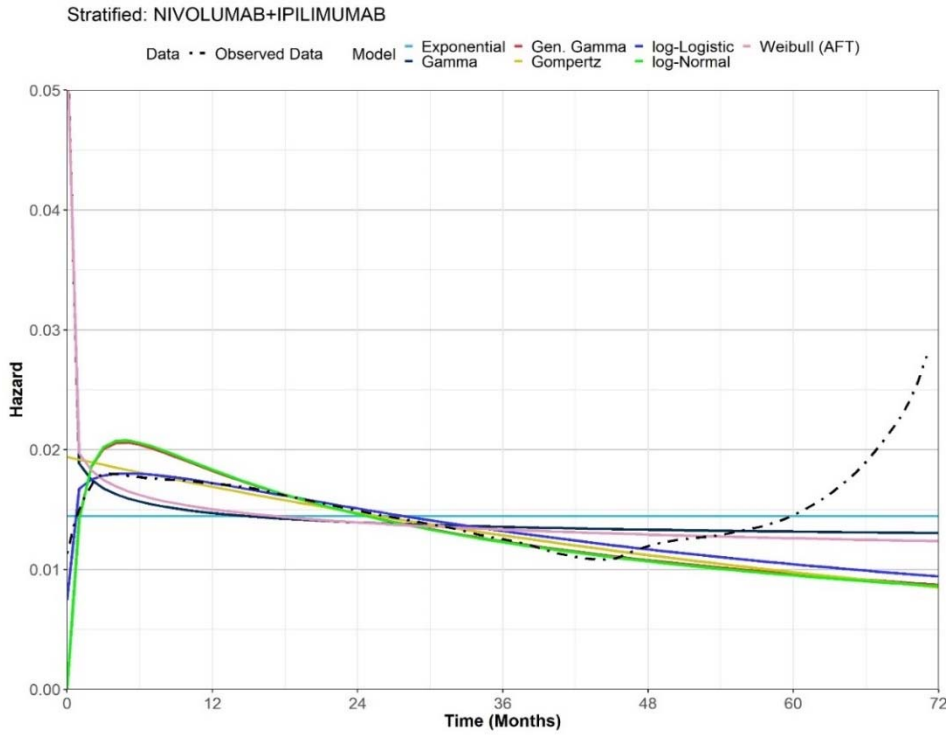




### *A.15.2.2 Model selection*

**Figure 19: NIVO+IPI smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up)**

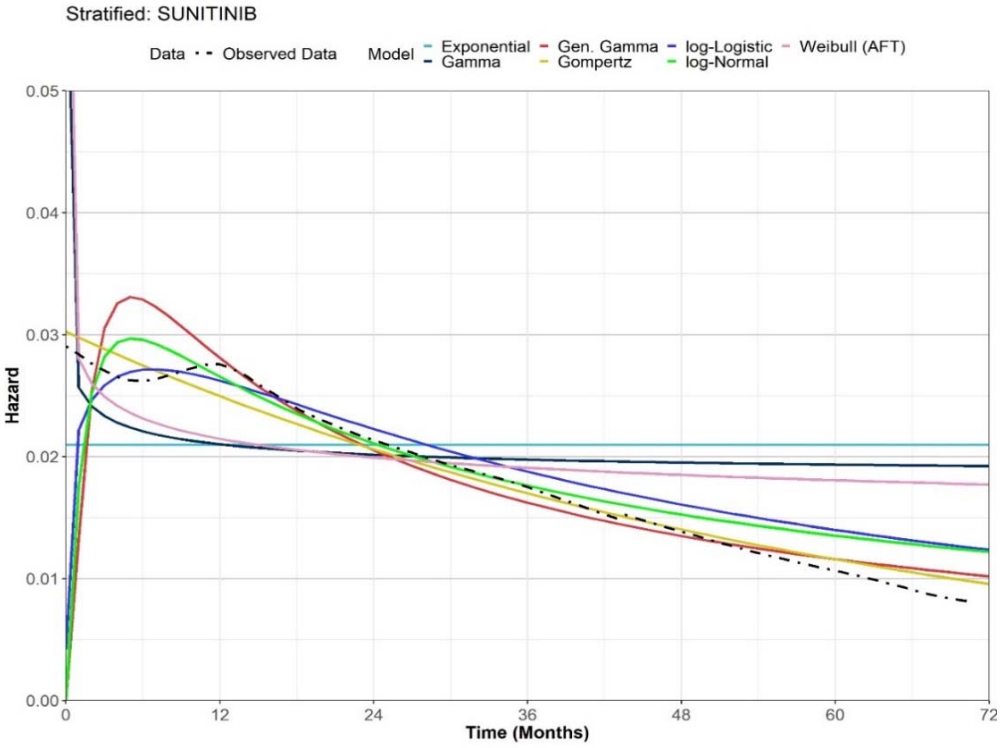



**Notes:** A 12 month smoothing interval was used for hazard data plots. The spike at the end is an artefact of censoring combined with the smoothing interval and should not be used to inform curve selection.



**Figure 20: Sunitinib smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month data cut)**




**Notes:** A 12 month smoothing interval was used for hazard data plots.



**Table 19: OS independent model fit statistics – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

| Model | Nivolumab+ipilimumab | | | | Sunitinib | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank |
| **Log-normal** | **2522.5** | **1** | **2530.6** | **1** | 2709.4 | 2 | **2717.5** | **1** | **5231.9** | **1** | **5248.1** | **1** |
| Gen. gamma | 2524.4 | 2 | 2536.6 | 4 | **2708.1** | **1** | 2720.2 | 2 | 5232.5 | 2 | 5256.8 | 2 |
| Log-logistic | 2526.5 | 3 | 2534.6 | 2 | 2718.6 | 3 | 2726.7 | 3 | 5245.1 | 3 | 5261.3 | 3 |
| Gompertz | 2528.1 | 4 | 2536.2 | 3 | 2725.4 | 4 | 2733.5 | 4 | 5253.5 | 4 | 5269.7 | 4 |
| Weibull (AFT) | 2534.6 | 5 | 2542.7 | 6 | 2743.0 | 5 | 2751.1 | 6 | 5277.6 | 5 | 5293.8 | 6 |
| Gamma | 2536.1 | 6 | 2544.3 | 7 | 2746.1 | 6 | 2754.2 | 7 | 5282.2 | 6 | 5298.4 | 7 |
| Exponential | 2536.9 | 7 | 2540.9 | 5 | 2746.2 | 7 | 2750.3 | 5 | 5283.1 | 7 | 5291.2 | 5 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion.
**Notes:** Models sorted by overall AIC score. Best fitting curve by AIC/BIC rank highlighted in bold and green; worst fitting curve highlighted in orange

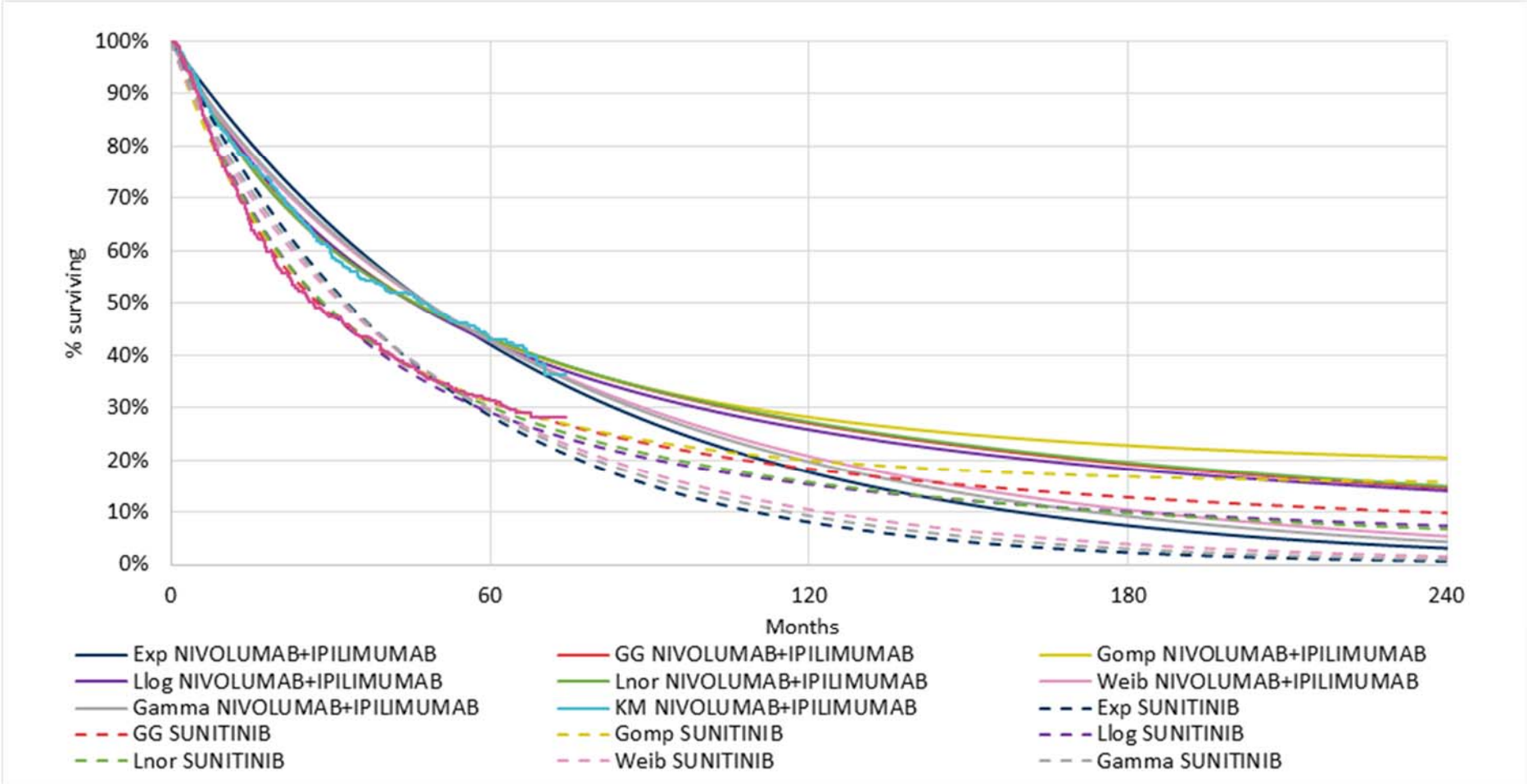
**Table 20: OS extrapolations independent model fit– CheckMate 214 intermediate/poor risk patients (60-month data cut)**

| Model | Survival % | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 years | | 10 years | | 15 years | | 20 years | |
| | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |
| Log-normal | 43.3 | 30.2 | 27.3 | 15.7 | 19.5 | 9.8 | 14.9 | 6.8 |
| Gen. gamma | 43.2 | 31.1 | 27.0 | 18.3 | 19.2 | 12.8 | 14.6 | 9.8 |
| Log-logistic | 42.5 | 29.1 | 25.8 | 15.3 | 18.3 | 10.1 | 14.0 | 7.4 |
| Gompertz | 43.1 | 31.2 | 28.2 | 19.9 | 22.8 | 16.8 | 20.5 | 15.8 |
| Weibull (AFT) | 42.8 | 29.7 | 20.7 | 10.5 | 10.4 | 3.9 | 5.4 | 1.5 |
| Gamma | 42.7 | 29.3 | 19.7 | 9.3 | 9.2 | 3.0 | 4.3 | 1.0 |
| Exponential | 42.0 | 28.5 | 17.7 | 8.1 | 7.4 | 2.3 | 3.1 | 0.7 |



**Figure 21: OS parametric model extrapolations – CheckMate 214 intermediate/poor risk patients (60-month data cut)**





### A.15.3 KM Progression-free survival – CheckMate 214

**Figure 22: PFS per IRRC (secondary definition); 17.5-month data cut**

#### *A.15.3.1 Assessing proportional hazards and accelerated failure time*

The log-cumulative hazard plot (Figure 23), the KM curve (Figure 3) and the Schoenfeld residual plot (Figure 24) were used to assess the plausibility of a PH assumption. All three plots show evidence that the PH assumption is not supported with the Schoenfeld residual test being rejected ($P < 0.01$) and a clear trend with time in Figure 24 and crossing of the log-cumulative hazards plots in Figure 23. Therefore, independent models were chosen as the base-case.



**Figure 23: Log-cumulative hazard plot for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Figure 24: Schoenfeld residual plot for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 25: Quantile-quantile plot for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

*A.15.3.2 Model selection*

**Figure 26: NIVO+IPI smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 27: Sunitinib smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Notes:** A 12 month smoothing interval was used for hazard data plots.

**Figure 28: NIVO+IPI smoothed hazard plots for and fitted spline models for PFS per IRRC (secondary definition) (1 knot) – CheckMate 214 (60-month data cut)**

**Notes:** A 12 month smoothing interval was used for hazard data plots.



**Figure 29: Sunitinib smoothed hazard plots for and fitted spline models for PFS per IRRC (secondary definition) (1 knot) – CheckMate 214 (60-month data cut)**

**Figure 30: NIVO+IPI smoothed hazard plots for and fitted spline models for PFS per IRRC (secondary definition) (2 knot) – CheckMate 214 (60-month data cut)**



**Figure 31: Sunitinib smoothed hazard plots for and fitted spline models for PFS per IRRC (secondary definition) (2 knot) – CheckMate 214 (60-month data cut)**



**Table 21: PFS independent model fit statistics – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

| Model | Nivo + ipi | | | | Sunitinib | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank |
| Hazard (2 knot) | 2382.3 | 1 | 2398.6 | 1 | 2636.7 | 1 | 2652.9 | 1 | 5019.1 | 1 | 5051.5 | 1 |
| Odds (2 knot) | 2382.9 | 2 | 2399.1 | 2 | 2642.7 | 2 | 2658.9 | 3 | 5025.6 | 2 | 5058.0 | 2 |
| Normal (1 knot) | 2388.1 | 4 | 2400.3 | 3 | 2647.4 | 4 | 2659.6 | 5 | 5035.5 | 3 | 5059.8 | 3 |
| Normal (2 knot) | 2387.3 | 3 | 2403.5 | 4 | 2648.9 | 6 | 2665.0 | 7 | 5036.2 | 4 | 5068.6 | 5 |
| Gen. gamma | 2391.9 | 5 | 2404.1 | 5 | 2649.1 | 7 | 2661.2 | 6 | 5041.0 | 5 | 5065.3 | 4 |
| Hazard (1 knot) | 2399.0 | 7 | 2411.1 | 7 | 2647.2 | 3 | 2659.3 | 4 | 5046.2 | 6 | 5070.5 | 6 |
| Odds (1 knot) | 2394.1 | 6 | 2406.3 | 6 | 2653.1 | 8 | 2665.3 | 8 | 5047.2 | 7 | 5071.5 | 7 |
| log-normal | 2441.5 | 8 | 2449.6 | 8 | 2648.2 | 5 | 2656.3 | 2 | 5089.7 | 8 | 5105.9 | 8 |
| Log-logistic | 2458.8 | 10 | 2466.9 | 10 | 2659.6 | 9 | 2667.7 | 9 | 5118.4 | 9 | 5134.6 | 9 |
| Gompertz | 2450.2 | 9 | 2458.3 | 9 | 2684.0 | 10 | 2692.1 | 10 | 5134.2 | 10 | 5150.3 | 10 |
| Weibull (AFT) | 2513.3 | 11 | 2521.4 | 11 | 2697.3 | 11 | 2705.4 | 12 | 5210.6 | 11 | 5226.8 | 11 |
| Gamma | 2533.4 | 12 | 2541.5 | 12 | 2700.5 | 13 | 2708.6 | 13 | 5233.9 | 12 | 5250.1 | 12 |
| Exponential | 2574.6 | 13 | 2578.7 | 13 | 2698.9 | 12 | 2702.9 | 11 | 5273.5 | 13 | 5281.6 | 13 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion.
**Notes:** Models sorted by overall AIC score. Best fitting curve by AIC/BIC rank highlighted in green; worst fitting curve highlighted in orange



**Figure 32: PFS extrapolations splines NIVO+IPI 1-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 33: PFS extrapolations splines sunitinib 1-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 34: PFS extrapolations splines NIVO+IPI 2-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 35: PFS extrapolations splines sunitinib 2-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



### A.15.4 Time to treatment discontinuation – CheckMate214

**Figure 36: KM curve of TTD by treatment arm – CheckMate 214 intermediate/poor risk patients (30-month minimum follow-up)**



**Figure 37: Swimmer plots for complete responders (per IRRC, CheckMate 214 60-month data) – NIVO+IPI (left) and sunitinib (right)**



**Figure 38: Swimmer plots for partial responders (per IRRC, CheckMate 214 60-month data) – NIVO+IPI (left) and sunitinib (right)**



### *A.15.4.1 Assessing proportional hazards and accelerated failure time*

The log-cumulative hazard plot (Figure 39), the KM curve (Figure 4) and the Schoenfeld residual plot (Figure 41) were used to assess the plausibility of a PH assumption for TTD. All three plots show evidence that the PH assumption may be violated with the global Schoenfeld residual test ($p < 0.01$) being rejected and a clear trend with time in Figure 40, and crossing of the log-cumulative hazards plots in Figure 39. Therefore, independent models were chosen as the base-case. The points on the QQ plot do not form a linear relationship (Figure 41), suggesting the accelerated failure time modelling assumption may not be supported.

**Figure 39: Log-cumulative hazard plot for TTD – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 40: Schoenfeld residual plot for TTD – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Figure 41: QQ plot for TTD – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



### *A.15.4.2 Model selection*

**Figure 42: NIVO+IPI smoothed hazard plots for TTD and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Notes:** A 12 month smoothing interval was used for hazard data plots.



**Figure 43: Sunitinib smoothed hazard plots for TTD and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Notes:** A 12 month smoothing interval was used for hazard data plots.



**Figure 44: NIVO+IPI smoothed hazard plots for TTD and fitted spline models (1-knot) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Key:** haz, hazard; k, knot; TTD, time to treatment discontinuation.



**Figure 45: Sunitinib smoothed hazard plots for TTD and fitted spline models (1-knot) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Key:** haz, hazard; k, knot; TTD, time to treatment discontinuation.



**Figure 46: NIVO+IPI smoothed hazard plots for TTD and fitted spline models (2-knot) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Key:** haz, hazard; k, knot; TTD, time to treatment discontinuation.



**Figure 47: Sunitinib smoothed hazard plots for TTD and fitted spline models (2-knot) – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

**Key:** haz, hazard; k, knot; TTD, time to treatment discontinuation.



**Table 22: TTD independent model fit statistics – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

| Model | NIVO+IPI | | | | Sunitinib | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank | AIC | AIC rank | BIC | BIC rank |
| Normal (2 knots) | 2913.2 | 1 | 2929.4 | 3 | 2775.1 | 5 | 2791.2 | 8 | 5688.2 | 1 | 5720.5 | 6 |
| Hazard (1 knot) | 2918.2 | 6 | 2930.3 | 5 | 2770.6 | 1 | 2782.7 | 1 | 5688.8 | 2 | 5713.0 | 1 |
| Hazard (2 knots) | 2916.4 | 4 | 2932.6 | 8 | 2772.5 | 3 | 2788.7 | 6 | 5688.9 | 3 | 5721.2 | 7 |
| Normal (1 knot) | 2915.6 | 2 | 2927.7 | 1 | 2773.4 | 4 | 2785.5 | 4 | 5689.0 | 4 | 5713.2 | 2 |
| Gen. gamma | 2918.8 | 7 | 2930.9 | 6 | 2772.4 | 2 | 2784.5 | 2 | 5691.2 | 5 | 5715.4 | 3 |
| Odds (2 knots) | 2917.5 | 5 | 2933.7 | 9 | 2777.3 | 7 | 2793.5 | 10 | 5694.9 | 6 | 5727.2 | 8 |
| Odds (1 knot) | 2916.1 | 3 | 2928.2 | 2 | 2779.0 | 9 | 2791.0 | 7 | 5695.0 | 7 | 5719.3 | 5 |
| Log-logistic | 2923.8 | 9 | 2931.9 | 7 | 2777.6 | 8 | 2785.6 | 5 | 5701.4 | 8 | 5717.5 | 4 |
| Weibull (AFT) | 2921.5 | 8 | 2929.6 | 4 | 2797.9 | 11 | 2806.0 | 11 | 5719.4 | 9 | 5735.6 | 9 |
| Log-Normal | 2949.5 | 12 | 2957.6 | 12 | 2777.3 | 6 | 2785.4 | 3 | 5726.8 | 10 | 5743.0 | 10 |
| Gompertz | 2944.1 | 11 | 2952.2 | 11 | 2784.4 | 10 | 2792.4 | 9 | 5728.5 | 11 | 5744.6 | 11 |
| Gamma | 2935.3 | 10 | 2943.4 | 10 | 2802.6 | 13 | 2810.6 | 13 | 5737.9 | 12 | 5754.1 | 12 |
| Exponential | 3036.1 | 13 | 3040.2 | 13 | 2802.4 | 12 | 2806.4 | 12 | 5838.5 | 13 | 5846.6 | 13 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion.
**Notes:** Models sorted by overall AIC score. Best fitting curve by AIC/BIC rank highlighted in green; worst fitting curve highlighted in orange



**Figure 48: TTD parametric model extrapolations – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 49: TTD extrapolations spline models NIVO+IPI 1-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 50: TTD extrapolations sunitinib spline models 1-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



**Figure 51: TTD extrapolations spline models NIVO+IPI 2-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**

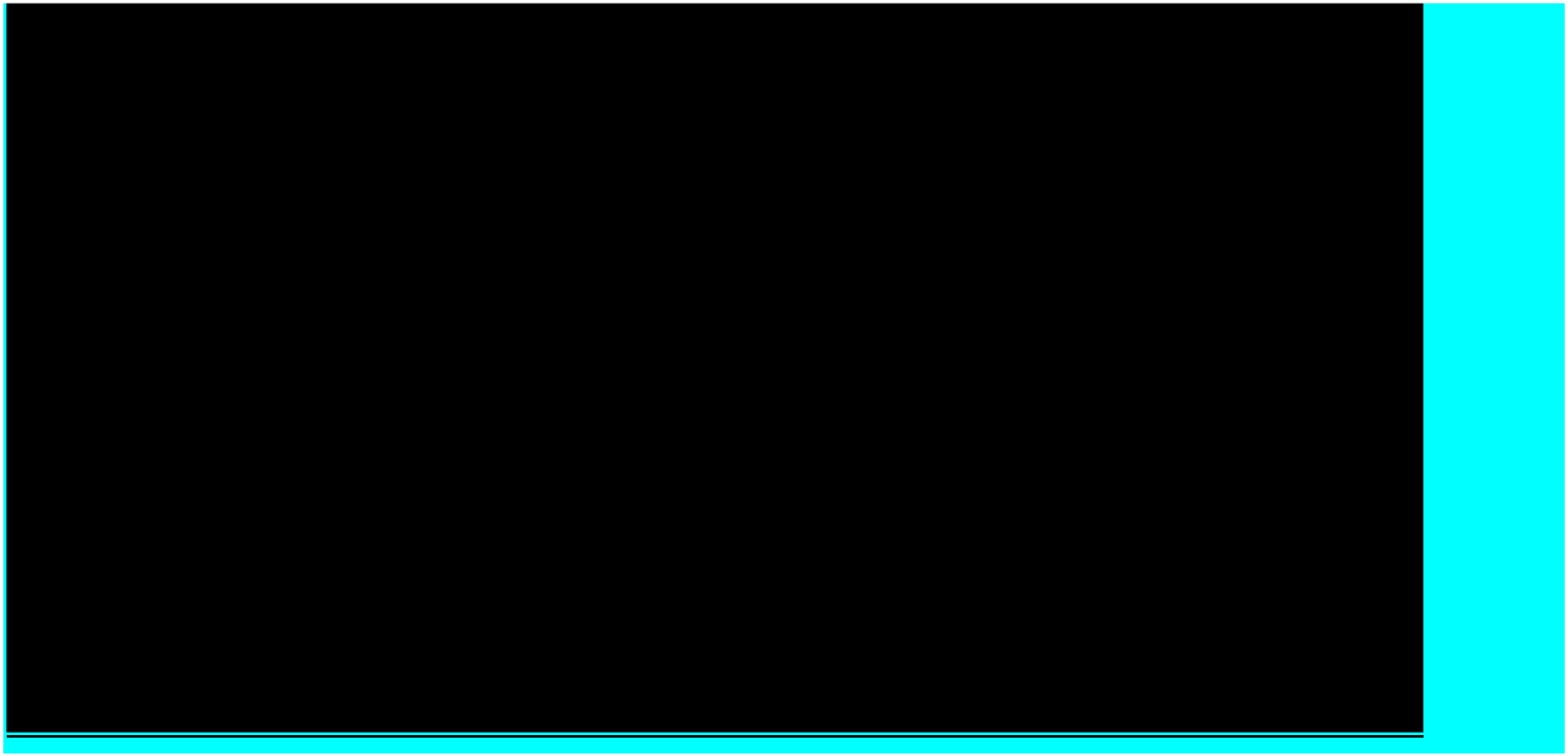




**Figure 52: TTD extrapolations spline models sunitinib 2-knot – CheckMate 214 intermediate/poor risk patients (60-month data cut)**



### A.15.5 Step-wise variable selection approach to mixed model analysis of CheckMate214

**Table 23: 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 Treatment arm and interactions to Model 6 |
| Intercept | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment arm (sunitinib) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Progression Status (Progression) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment Status (Off treatment) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment Arm*Progression Status | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |



| | **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 Treatment arm and interactions to Model 6 |
| Treatment Arm*Treatment Status | | | | | | | |
| Progression Status*Treatment Status | | | | | | | |
| Treatment Arm*Progression Status*Treatment Status | | | | | | | |
| -2 Log Likelihood | | | | | | | |
| AIC (smaller is better) | | | | | | | |
| BIC (smaller is better) | | | | | | | |
| **Key:** AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EQ-5D-3L, EQ-5D 3-level questionnaire; SE, standard error. | | | | | | | |



### A.15.6 Cost-effectiveness model parameters

**Table 24: Cost-effectiveness model parameters**

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| **Controls** | | | |
| Cycle length (weeks) | 1.00 | Not included in SA | Unchanged from original appraisal |
| Cycles per year | 52.18 | Not included in SA | |
| Time Horizon (years) | 40.00 | Not included in SA | |
| Discount rate used for costs | 3.50% | Not included in SA | |
| Discount rate used for QALYs | 3.50% | Not included in SA | |
| Discount rate used for Life Years | 0.00% | Not included in SA | |
| Cycle length as a proportion of a year | 1.92% | Not included in SA | |
| **Drug Costs** | | | |
| Nivolumab drug costs (100mg formulation) | [redacted] | Not included in SA | Unchanged from original appraisal |
| 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] | Triangular (0.87,1) | Unchanged from original appraisal |
| Proportion of doses of ipililumab treatment received | [redacted] | Triangular (0.84,1) | |
| 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] | |
| 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] | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| Proportion of doses of subsequent cabozantinib received | [redacted] | [redacted] | |
| Proportion of doses of subsequent everolimus received | [redacted] | [redacted] | |
| **Admin and Health State Costs** | | | |
| One-off progression costs | £0.00 | Not included in SA | Unchanged from original appraisal |
| 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) | |
| Nivolumab administration cost - subsequent visits | £310.00 | Gamma (252.23,373.63) | |
| Ipilimumab administration cost | £0.00 | Gamma (0,0) | |
| Sunitinib administration cost | £164.00 | Gamma (133.44,197.67) | |
| Pazopanib administration cost | £164.00 | Gamma (133.44,197.67) | |
| **Adverse Event Costs** | | | |
| Cost of treating adverse event Anaemia | £280.03 | Gamma (227.84,337.52) | Unchanged from original appraisal |
| 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) | |
| Cost of treating adverse event Lipase increased | £280.03 | Gamma (227.84,337.52) | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| 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 erythrodysaesthesia 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) | Unchanged from original appraisal |
| 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) | |
| Average length of subsequent nivolumab TOT (weeks) | [redacted] | [redacted] | |
| 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 NIVO+IPI patients receiving subsequent therapy | [redacted] | [redacted] | Section A.7.6 |
| Proportion of sunitinib patients receiving subsequent therapy | [redacted] | [redacted] | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| Proportion of patients from NIVO+IPI receiving subsequent NIVO | [redacted] | Dirichlet (PSA only) | Section A.7.6 |
| Proportion of patients from NIVO+IPI receiving subsequent Sunitinib | [redacted] | | |
| Proportion of patients from NIVO+IPI receiving subsequent Pazopanib | [redacted] | | |
| Proportion of patients from NIVO+IPI receiving subsequent Axitinib | [redacted] | | |
| Proportion of patients from NIVO+IPI receiving subsequent Cabozantinib | [redacted] | | |
| Proportion of patients from NIVO+IPI receiving subsequent Everolimus | [redacted] | | |
| Proportion of patients from Sunitinib receiving subsequent NIVO | [redacted] | Dirichlet (PSA only) | Section A.7.6 |
| Proportion of patients from Sunitinib receiving subsequent Sunitinib | [redacted] | | |
| Proportion of patients from Sunitinib receiving subsequent Pazopanib | [redacted] | | |
| Proportion of patients from Sunitinib receiving subsequent Axitinib | [redacted] | | |
| Proportion of patients from Sunitinib receiving subsequent Cabozantinib | [redacted] | | |
| Proportion of patients from Sunitinib receiving subsequent Everolimus | [redacted] | | |
| Proportion of patients from Pazopanib receiving subsequent NIVO | [redacted] | Dirichlet (PSA only) | Section A.7.6 |
| Proportion of patients from Pazopanib receiving subsequent Sunitinib | [redacted] | | |
| Proportion of patients from Pazopanib receiving subsequent Pazopanib | [redacted] | | |
| Proportion of patients from Pazopanib receiving subsequent Axitinib | [redacted] | | |
| Proportion of patients from Pazopanib receiving subsequent Cabozantinib | [redacted] | | |
| Proportion of patients from Pazopanib receiving subsequent Everolimus | [redacted] | | |
| **Health State Utilities** | [redacted] | | |
| CM214 Mixed model parameter, Constant | [redacted] | [redacted] | Section A.6.1.7 and A.7.7 |
| CM214 Mixed model parameter, Decrement - treatment arm (sunitinib) | [redacted] | [redacted] | |
| CM214 Mixed model parameter, Decrement - progression status (Not progressed) | [redacted] | [redacted] | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| [redacted] | | | |
| CM214 Mixed model parameter, Decrement -treatment status (off treatment) | [redacted] | [redacted] | |
| CM214 Mixed model parameter, Decrement – interaction; treatment arm and progression status | [redacted] | [redacted] | |
| CM214 Mixed model parameter, Decrement – interaction; treatment arm and treatment status | [redacted] | [redacted] | |
| CM214 Mixed model parameter, Decrement – interaction; treatment status and progression status | [redacted] | [redacted] | |
| CM214 Mixed model parameter, Decrement – interaction; treatment arm, progression status and treatment status | [redacted] | [redacted] | |
| **Adverse Event Disutilities** | | | |
| Utility decrement for adverse event Anaemia | -0.08 | Normal (-0.07,-0.1) | Unchanged from original appraisal |
| Utility decrement for adverse event Asthenia | -0.20 | Normal (-0.16,-0.24) | |
| 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 erythrodysaesthesia syndrome | -0.04 | Normal (-0.03,-0.05) | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| 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) | Unchanged from original appraisal |
| 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 erythrodysaesthesia 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 | CI (distribution) | See Section |
|---|---|---|---|
| Cycle probability for nivolumab+ipilimumab of adverse event Thrombocytopenia | 0.00 | Beta (0,0) | |
| Cycle probability for nivolumab+ipilimumab of adverse event Vomiting | 0.00 | Beta (0,0) | |
| Cycle probability for sunitinib of adverse event Anaemia | 0.00 | Beta (0,0.01) | Unchanged from original appraisal |
| 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 (0,0.01) | |
| 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 erythrodysaesthesia syndrome | 0.00 | Beta (0,0.01) | |
| Cycle probability for sunitinib of adverse event Pruritus | 0.00 | Beta (0,0) | |
| Cycle probability for sunitinib of adverse event Rash | 0.00 | Beta (0,0) | |
| Cycle probability for sunitinib of adverse event Stomatitis | 0.00 | Beta (0,0.01) | |
| Cycle probability for sunitinib of adverse event Thrombocytopenia | 0.00 | Beta (0,0.01) | |
| Cycle probability for sunitinib of adverse event Vomiting | 0.00 | Beta (0,0) | |
| **Survival Parameters - PFS** | 0.00 | Not included in SA | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ0(nivolumab+ipilimumab) | [redacted] | Multivariate normal (PSA only) | Section A.7.4 |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ1(nivolumab+ipilimumab) | [redacted] | | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ2(nivolumab+ipilimumab) | [redacted] | | |



| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| PFS Independent Spline 2 knots - hazard - gamma 1 γ3(nivolumab+ipilimumab) | [redacted] | | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ0 (sunitinib) | [redacted] | | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ1 (sunitinib) | [redacted] | | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ2 (sunitinib) | [redacted] | | |
| PFS Independent Spline 2 knots - hazard - gamma 1 γ3 (sunitinib) | [redacted] | | |
| **Survival Parameters - TTD** | | | |
| [redacted] | [redacted] | Multivariate normal (PSA only) | Section A.7.5 |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | | |
| **Survival Parameters - OS** | | | |
| OS Independent Log-normal meanlog(nivolumab+ipilimumab) | 3.82 | Multivariate normal (PSA only) | Section A.7.3 |
| OS Independent Log-normal sdlog(nivolumab+ipilimumab) | 1.59 | | |
| OS Independent Log-normal meanlog (sunitinib) | 3.36 | | |
| OS Independent Log-normal sdlog (sunitinib) | 1.42 | | |



### A.15.7 Cost-effectiveness model corrections and changes

The economic model used in the previous submission to provide ICERs for CDF entry ('1182 NIVO+IPI ERG critique ACD response_21 Jan 2019 [ACIC]') was used as a base for the revised model for the CDF review submission. The following changes were made to ensure model transparency and ease of use:

- Addition of CheckMate 214 (60-month) KM data and parametric survival extrapolations for OS, PFS and TTD to a new 'Curve Selections' sheet
- Addition of CheckMate 214 (60-month) and SACT subsequent therapy proportions as an option in the 'Disease and AE Resources' sheet
- Addition of CheckMate 214 60-month utility analyses in the 'Utilities' sheet
- New switches in the 'Controls' sheet to allow for selection of data source, model corrections and budget impact population inputs
  - On further review of the model, an error was identified in the disease management costs calculations, whereby the progression-free resource use parameter was not read correctly into the 'PF NivoIpi' sheet. This new switch corrects for this error
- Update of company base case settings in the 'Controls' sheet

### A.15.8 Clinical validation

Key modelling assumptions were validated with two clinicians at a 1 hour 30 minute teleconference meeting on 18th August 2021.[7] Dr Richard Griffiths (Clatterbridge Cancer Centre) and Dr Naveen Vasudev (University of Leeds/St James's Institute of Oncology) were asked questions regarding patient characteristics in clinical practice, subsequent treatments received by patients, and expectations for treatment duration, progression-free survival and OS. Meeting notes were written up and approved by both clinicians before being submitted with the questions asked alongside this dossier in the reference pack.



### A.15.9 Impact of COVID-19 pandemic on SACT data

It should also be considered that clinical outcomes and the characteristics of patients in SACT may have also been affected by the coronavirus disease 2019 (COVID-19) pandemic. Although the clinicians interviewed for validation are both based at larger centres, where the impact of external factors such as COVID on patient care would likely be lower than that of a less specialist centre, both suggested that COVID still had some, although marginal, impact on patient treatment at the height of the pandemic.[7] As evidenced by the Cancer Research UK report, 29% of patients reported their oncology treatment having been affected in at least one way due to COVID (a delay, cancellation or change to their expected treatment, with an average wait time of 13.4 weeks for testing and 13.5 weeks for treatment) [16], and a study by the Nuffield Trust demonstrated that urological cancer referrals, consultant appointments and diagnoses all suffered months with greater than 50% reductions on pre-pandemic levels within the data collection period from SACT.[17] This is likely to have resulted in sicker patients being included in the SACT dataset and poorer treatment outcomes.



### A.15.10 Efficacy data from CheckMate 214 intermediate-/poor-risk patients with OS of at least 5 years

**Figure 53: Swimmer plots for complete responders with OS of at least 5 years (per IRRC, CheckMate 214 60-month data) – NIVO+IPI (left) and sunitinib (right)**



**Figure 54: Swimmer plots for partial responders with OS of at least 5 years (per IRRC, CheckMate 214 60-month data) – NIVO+IPI (left) and sunitinib (right)**



**Figure 55: PFS by best overall response per IRRC, secondary definition, in patients with OS of at least 5 years, CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**



# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Cancer Drugs Fund review

# Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

## Clarification questions

**September 2021**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID3880_Nivo+ipi for RCC_clarification letter_for company 23092021_HS [CIC] | | Yes | 23/09/21 |

**Notes for company**

**Highlighting in the template**

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.

**To delete grey highlighted text, click anywhere within the text and press DELETE.**

# Section A: Clarification on effectiveness data

***Not applicable***

# Section B: Clarification on cost-effectiveness data

**B1. <u>Priority question</u>.** Please provide justification for why the economic model generates lower mortality rates for NIVO+IPI compared to sunitinib after year 4, given that data from the CheckMate 214 trial suggest that mortality rates for both arms have equalised, or have become lower for sunitinib, by the end of year 4 (as shown in Table 1).

Table 1 Annual mortality rates from the CheckMate 214 trial

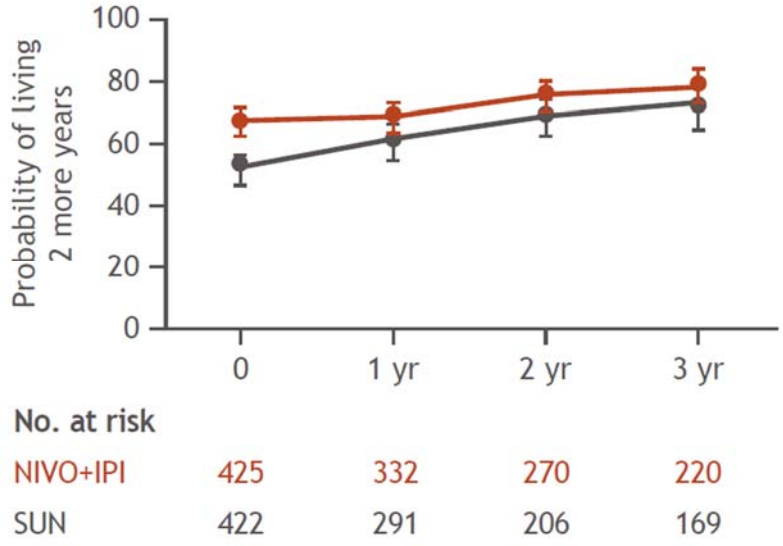
| Year | NIVO+IPI | Sunitinib |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |

Source: ERG calculated rates using data from CS, Table 5

BMS disagree with the idea that the CheckMate 214 trial data suggests that mortality rates for both arms have equalized, or have become lower for sunitinib, by the end of year 4 based on the clinical evidence presented in the company submission. It is inappropriate to assume an equal hazard of death after a certain timepoint, not only because the subsequent treatments available in the second line setting are different across the two treatment arms, but also because there is a much higher proportion of patients who have not yet progressed in the NIVO+IPI arm than the sunitinib arm, where their disease has worsened. In addition, BMS believes that this assumption is not clinically plausible as it would contradict the available evidence where NIVO+IPI demonstrates a sustained, statistically significant improvement in survival compared to sunitinib and continues to have substantial benefits in terms of other efficacy outcomes, as demonstrated throughout section A.6.1 in the company submission. Furthermore, BMS believe implementation of such an assumption to the economic analyses from 4 years over a lifetime horizon would be clinically implausible and scientifically inappropriate.

Conditional survival analysis using the 60-month follow-up data from CheckMate 214 also show that for 0 to 3 years, the likelihood of surviving 2 or more years (i.e. up to 5 years) increases for both arms over time; however, at all time points, conditional survival remains greater for NIVO+IPI patients than for sunitinib patients (Figure 1)[1]

**Figure 1: CheckMate 214 conditional overall survival (minimum 60-month follow-up)**




Patients in the NIVO+IPI arm of CheckMate 214 are continuing to benefit from the treatment, as median duration of response (DoR) has not been met for NIVO+IPI while median DoR was previously reported for sunitinib as 19.7 months ([redacted]).[1] This means there is a minimum gain in median DoR of at least [redacted] months. The probability of being in response at 60 months is [redacted] for NIVO+IPI versus [redacted] for sunitinib, and the conditional probability of remaining in response with NIVO+IPI for an additional 2 years beyond first response increased from 0 (at first confirmed response) to 90% at year 3 for NIVO+IPI patients.[1] Therefore, to assume an equal hazard of death from 4 years based on OS rates alone would ignore the substantial benefit in terms of continued response that patients are experiencing in the NIVO+IPI arm that is not observed in the sunitinib arm. In addition, the equal hazard of death assumption would rely on a further assumption that continuing to be in response has no long-term benefit.

With further data cuts, progression-free survival (PFS) benefit has continued to improve over the sunitinib treatment arm, with the hazard of progression (or death) trending toward [redacted] for NIVO+IPI, while it [redacted] that remains [redacted] for sunitinib (Figure 26 and Figure 27 in the company submission). From year 3, NIVO+IPI PFS remains fairly stable; of the patients who were progression-free at 2 years ([redacted] and [redacted] in NIVO+IPI and sunitinib arms, respectively), [redacted] remained

progression-free at 5 years with NIVO+IPI than with sunitinib ([redacted] versus [redacted], respectively). The 5-year PFS probability was [redacted] greater with NIVO+IPI when compared with SUN ([redacted] versus [redacted]), and only [redacted] of patients in the NIVO+IPI arm are still on first-line therapy, while a greater proportion of patients have received subsequent treatment in the sunitinib arm than NIVO+IPI arm.

Of patients who remained alive at 5 years in either arm, [redacted] were progression-free with NIVO+IPI versus [redacted] with sunitinib, and in those patients alive at 5 years who had achieved a response with first-line therapy (partial response [PR] or complete response [CR]), [redacted] of sunitinib patients have received subsequent therapy compared with [redacted] of NIVO+IPI patients, further supporting the unique durable response seen with NIVO+IPI. In patients alive at 5 years, median PFS [redacted](CR rate: 11.3% for NIVO+IPI versus 2.1% for sunitinib) [redacted] in the NIVO+IPI arm[redacted]in the sunitinib arm, reflecting a minimum gain in median PFS for patients who received NIVO+IPI and achieved a PR of at least [redacted] months.

While the extent to which PFS impacts OS is uncertain and remains unestablished for immunotherapy combinations in first line renal cell carcinoma, an equal hazard of death assumption from 4 years would imply that there is no further longer-term survival benefit for patients who remain progression-free versus those who have progressed. In addition, an equal hazard of death would also mean no longer-term benefit for patients who may also be off-treatment and still in response or progression-free over patients who have already progressed and may be receiving second-line (or later-line) therapy. BMS believe such an assumption to be clinically implausible.

The mortality rates for NIVO+IPI and sunitinib used in the economic model are a function of the best-fitting survival models fitted to the CheckMate 214 data. Overall survival, derived from CheckMate 214, was modelled using standard methodologies and based on guidance from the NICE Decision Support Unit (DSU), and is modelled using individual patient-level data, rather than annual changes to the proportion of patients remaining alive as provided in the table in the question above.[2] The suitability of standard parametric fits were assessed using methods described in the submission, namely statistical fit criteria (AIC/BIC), smoothed hazard plots, log-cumulative hazards plots, clinical validity and assessment of visual fit. Sufficient changes in the shape of

the hazard function were not observed in the log-cumulative hazards plots or the smoothed hazard plots (Figure 16, 19 and 20 from the company evidence submission), to warrant such a piecewise modelling approach adjusting hazards of survival curves. Given the limitations of piecewise approaches to survival modelling[3], and lack of clear rationale for using these methods, the mortality rates are informed by the pattern observed and extrapolated from the entirety of the CheckMate 214 OS data.

This question arose from the data highlighted in Table 1, looking at an annual relative mortality rate for NIVO+IPI and sunitinib as produced by the ERG. At the clinical validation meeting conducted by the company for the CDF resubmission, clinical experts stated that they expected decreasing hazards over time across both treatment arms from CheckMate 214, suggesting that sharp increases in mortality would not be expected, and that they expected disease-related mortality to cease after 10 years.[4] Indeed, the overall survival smoothed hazard plots for the 48-month and 60-month minimum follow-up datacuts (Figure 2) highlight decreasing hazards over time across both arms, with NIVO+IPI consistently remaining below sunitinib for the majority of follow-up. In Figure 2, when plotting both the hazards of the 48-month data cut and the 60-month minimum follow-up data cut, up to 48 months only, the two curves (48- and 60-month curves) [redacted] the end of the curve. For NIVO+IPI, this is not the case when the 60-month minimum follow-up data is plotted up to 60 months (see Figure 2), which results in a [redacted] towards the end of the curve. This [redacted] present at the end of the Kaplan-Meier curve, which cannot reliably be used or interpreted, particularly as we see events occurring in the heavily censored portion of the tail (see Figure 3), which are the cause for this artificial observed uptick at the end of the smoothed hazard. As such, any trends seen at the end of the data should be treated with extreme caution as the [redacted] in the 60-month data is likely to be [redacted]. It is clear from the plot of the 60-month data to 48 months only (Figure 2 [left]) that there is a [redacted] in the hazards between treatment arms at 48 months using the 60-month data cut, which does not support any assumption of equal hazard of death from 4 years.

It should also be noted that across the data cuts, and over the duration of available follow-up in the 60-month data cut, the mean hazard ratio (Table 8 in company submission and Figure 4) remains relatively stable and consistently below 1, with no sharp upward trend toward 1 at any time, which would have indicated a reduction in relative benefit for NIVO+IPI versus sunitinib. This demonstrates that NIVO+IPI, continues to provide improved sustained and significant OS benefit compared with sunitinib, with no indication for a substantial reduction in this relative benefit between treatments within the observed data.

**Figure 2 CheckMate 214 overall survival hazard plots for the 48-month and 60-month minimum follow-up data cuts, plotted up to 48-months (left) and up to 60 months (right)**

**Figure 3: CheckMate 214 overall survival smoothed for NIVO+IPI and sunitinib using the 48-month and 60-month data cuts, along with unsmoothed hazard plots for NIVO+IPI (left) and sunitinib (right)**

**Figure 4: CheckMate 214 overall survival: mean hazard ratio of NIVO+IPI relative to sunitinib over the observed time period (60-month minimum follow-up)**

**B2. <u>Priority question</u>. Please provide statistical evidence to support using different utility values in model health states for NIVO+IPI and sunitinib.**

Table 1 presents the step-wise regression analyses of EQ-5D-3L utility data from CM214 including p-values, as provided in the company evidence submission as Table 23 (Appendix). These show the statistical significance of [redacted] as a covariate in each of the tested models; in addition, significant interactions are observed between treatment arm, treatment status and progression status in model 7 suggesting that patient's quality of life is different depending on the treatment they receive and their health state.

**Table 1: Results from stepwise variable selection approach to mixed model analysis of CheckMate 214 intermediate-/poor-risk EQ-5D-3L utility data (Appendix A15.5, Table 23 from the company evidence submission)**

| | **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 Treatment arm and interactions to Model 6 |
| Intercept | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment arm (sunitinib) | | [redacted] | | | [redacted] | | [redacted] |
| Progression Status (Progression) | | | [redacted] | | | [redacted] | [redacted] |
| Treatment Status (Off treatment) | | | | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment Arm*Progression Status | | | | | | | [redacted] |
| Treatment Arm*Treatment Status | | | | | [redacted] | | [redacted] |
| Progression Status*Treatment Status | | | | | | [redacted] | [redacted] |
| Treatment Arm*Progression Status*Treatment Status | | | | | | | [redacted] |
| -2 Log Likelihood | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| AIC (smaller is better) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BIC (smaller is better) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EQ-5D-3L, EQ-5D 3-level questionnaire; SE, standard error.

Table 2 presents the 95% confidence intervals for the utility parameters. Given the multivariate nature of the utility model and the correlations between each parameter, the upper and lower bounds for each parameter were calculated by setting every parameter to their 2.5% or 97.5% limits. The confidence intervals presented in the table below are within a narrow window demonstrating the precision of the estimates.

As can be seen in the tables, [redacted] are a statistically significant parameter with a [redacted], demonstrating the support and confidence for the [redacted]

**Table 2: Utility parameter 95% confidence intervals**

| Utility Parameter | Lower Bound | Upper Bound |
|---|---|---|
| u_214.constant (Constant) | [redacted] | [redacted] |
| u_214.arm.dec (Decrement- treatment arm) | [redacted] | [redacted] |
| u_214.prog.dec (Decrement- progression status (Not progressed)) | [redacted] | [redacted] |
| u_214.treat.dec (treatment status (off-treatment)) | [redacted] | [redacted] |
| u_214.interaction.arm.pro.dec (Interaction; treatment arm and progression status) | [redacted] | [redacted] |
| u_214.interaction.arm.treat.dec (Interaction; treatment arm and treatment status) | [redacted] | [redacted] |
| u_214.interaction.prog.treat.dec (Interaction; treatment status and progression status) | [redacted] | [redacted] |
| u_214.interaction.arm.treat.prog.dec (Interaction; treatment arm, progression status and treatment status) | [redacted] | [redacted] |

**B3. <u>Priority question</u>. Please provide utility values based on pooled EQ-5D data from the NIVO+IPI and sunitinib arms of the CheckMate 214 trial.**

Given the results provided in Table 1, and the [redacted] on health state utilities, the use of pooled EQ-5D data from NIVO+IPI and sunitinib arms of CheckMate 214 is not supported. [redacted] was found to be a significant predictor of patient utility, with patients randomised to NIVO+IPI [redacted] to the sunitinib arm of CheckMate 214. Consistent with the results in the original appraisal preferred by the ERG and NICE committee, the selected model (Model 7) captures treatment arm, progression status and treatment status which are all statistically significant.

**B4. Priority question. Please provide the following Kaplan-Meier analyses:**

A. Time to death from any cause (OS)

B. PFS per IRRC (secondary definition)

C. Time to study treatment discontinuation (TTD)

Please use the following specifications:

| | |
|---|---|
| Trial data set: | CheckMate 214 |
| Format: | Please present analysis outputs using the format used in the sample table below |
| Populations: | (i) The population with poor risk including all patients lost to follow-up or withdrawing from the trial<br><br>(ii) The population with intermediate risk including all patients lost to follow-up or withdrawing from the trial |
| Trial arms: | (i) NIVO+IPI<br><br>(ii) Sunitinib |

***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 |

The CheckMate 214 trial was not powered to evaluate the efficacy of NIVO+IPI versus sunitinib in the intermediate- and poor-risk IMDC subgroups separately. The intermediate-risk and poor-risk population represented 78.6% (334 patients) and 21.4% (91 patients) of the enrolled intermediate- and poor-risk IMDC subgroup population in CheckMate 214, respectively. Analyses using the separated intermediate and poor risk subgroup is inappropriate as the licensed indication and final scope considered within this appraisal consider the combined intermediated- and poor- risk subgroup. Furthermore, the potential use of this separate KM data to investigate efficacy in a population with a similar distribution in IMDC risk score

observed in the SACT data would be scientifically inappropriate. Therefore, BMS disagree with providing the KM data for these subgroups separately.

In the original appraisal of NIVO+IPI in TA581, the ERG previously highlighted that the intermediate- and poor-risk RCC population subgroups separately "should be interpreted with caution, as the analyses were post-hoc analyses" and concluded "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." (See TA581 ERG Report Section 4.6.4 page 52). This is also in line with the final appraisal document (FAD) of the original submission which states "The committee concluded that the combined intermediate- or poor- risk group is appropriate for decision making." (see TA581 FAD section 3.4 page 4).

Furthermore, given the immaturity of the SACT data (5 months minimum follow-up), the timing upon which it was collected (during the COVID-19 pandemic), and the CDF Managed Access Agreement "Data collection via SACT will support data collected from the CheckMate 214 clinical trial." (see TA581 CDF Managed Access Agreement section 6.3 page 7), any decisions in this appraisal should be based on the CheckMate 214 data, as obtained from the trial in the population for which the study was powered (a combined intermediate/poor risk population). Any data based on SACT collection should be considered secondary (or exploratory) to the primary source of clinical effectiveness evidence that is CheckMate 214.

## *References*

[1] Motzer RJ, Tannir NM, McDermott DF, et al. 661P Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma. Volume 32, Supplement 5, S685-S687.

[2] Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. (Updated: March 2013) Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/pdf/PubMedHealth_PMH0089910.pdf. Accessed: 14 December 2017.

[3] Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis. 2020. Available at: http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf. Accessed: 30 July 2021.

[4] Bristol Myers Squibb. Nivolumab plus ipilimumab in renal cell carcinoma - Cancer Drugs Fund Exit Consult: Clinical validation. 2021. Data on File.

NICE National Institute for Health and Care Excellence

# Patient organisation submission

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

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. [Please note that declarations of interests relevant to this topic are compulsory].

**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 | [redacted] |
| 4a. Brief description of the organisation (including who funds it). How many members does it have? | Kidney cancer UK is a charity which provides help and support to kidney cancer patients and their families. We offer counselling services and support and advice to our patients on the careline, provide up to date information and education on the disease and treatments on our website, raise awareness, run campaigns, and fund research into kidney cancer.<br><br>The organisation is funded by donations and each month we communicate with approximately 3900 patients. Our website received 36,000 views per year. |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant | Yes -Bristol Myers Squibb-<br>Covid £10,000<br>Survey £2,000<br>Accord £5,000<br>Total: £17,000 |

| | |
|---|---|
| manufacturers are listed in the appraisal matrix.]<br><br>If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 4c. 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 listened to patients and their families views in the closed facebook support groups and in the Zoom support group meetings. I also gathered information from patients from talking to them on the careline, and from Q and A webinars and our patient survey. |
| **Living with the condition** | |
| 6. What is it like to live with the condition? What do carers | Being diagnosed with kidney cancer can be incredibly stressful for patients and their families, 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, |

| | |
|---|---|
| experience when caring for someone with the condition? | scans and procedures can be emotionally challenging. According to our recent annual survey patients with kidney cancer reported feeling anxious, emotionally low, abandoned after surgery and scared about their cancer returning. Knowledge that there are a variety of treatment options available to them will give patients and their carers some hope and comfort.<br><br>Patients reported having a range of symptoms from their cancer including fatigue, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease, which can be disabling for many and distressing for both patients and carers. This can affect their life in many ways, they may need to take regular pain medication to control their pain, many people report having less energy to carry out their activities of daily living and have needed to take time off work.<br><br>Side effects from treatment include fatigue, loss of appetite, nausea, night sweats and rashes, some even report being hospitalised with colitis or pneumonitis too. However, some people report that the drugs work for them and they have fewer side effects and they have no further disease spread which helps to improve their quality of life. 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 immunotherapy treatments. Current drug treatments for kidney cancer are very limited in number and have plenty of side effects. Side effects such as anemia, fatigue, weight loss, depression, nausea and skin conditions can really affect the patients quality of life. 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.<br><br>The introduction of nivolumab (immunotherapy) as a NICE recommended 2nd line drug was well received by patients and their families. Patients have reported back on how effective this drug has been for them, especially on how it improves 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? | Advantages of the treatment patient's and their carer's reported were;<br>• Disease control with no metastatic progression<br>• Prolonged survival rate<br>• Reduction in cancer pain and other cancer symptoms<br>• Improvement in their mental health knowing that their treatment is working<br>• Quality of life- living longer and having more time with family and friends |

| | |
|---|---|
| | • Family and friends feel reassured that their loved ones treatment is working<br>• Patients felt more in control of their lives on treatment |
| | |
| **Disadvantages of the technology** | |
| 10. What do patients or carers think are the disadvantages of the technology? | Disadvantages of a treatment might include:<br>• Poor disease control and metastatic progression<br>• No difference in survival rate<br>• Side effects such as fatigue, low mood, weight loss, poor appetite, urticaria, bone pain, elevated liver enzymes, and in rarer cases colitis and pneumonitis as reported by patients<br>• The patients may have to travel far to the hospital to receive their treatment<br>• Difficulties in taking or using the treatment (for example, receiving IV medication instead of tablets)<br>• Difficult for carers watching loved ones suffer from side effects of the treatment<br>• Financial impact of paying for travel to and from the hospital or paying for a carer to accompany them |
| | |

| | |
|---|---|
| **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 non-clear cell renal cell carcinoma?<br>Why are people not allowed to use the treatment again on the NHS if they have previously stopped it before due to being in remission? |

**Key messages**

15. In up to 5 bullet points, please summarise the key messages of your submission:

- People with advanced kidney cancer have limited 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.
- In time there will hopefully be more development in immunotherapy treatments and there will be better outcomes in survival rates and a better quality of life for patients living with advanced kidney cancer.
- How the drugs work varies for everyone. 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.

……

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NICE National Institute for Health and Care Excellence

**Professional organisation submission**

# Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3380]

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 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 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 13 pages.

| **About you** | |
|---|---|
| 1. Your name | [redacted] |
| 2. Name of organisation | NCRI-ACP-RCP-RCR |

| | |
|---|---|
| 3. Job title or position | [redacted] |
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☐ a specialist in the treatment of people with this condition?<br>☐ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | NCRI-ACP-RCP-RCR |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] | No |

| | |
|---|---|
| If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | No |
| **The aim of treatment for this condition** | |
| 6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | The main aims include improvement in median overall survival, long term survival, tumour shrinkage/response, prevention of progression, improvement of symptoms, and improvement in quality of life |
| 7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in | Significant response would be improvement by 3 months in median overall survival compared to standard of care sutent, a tyrosine kinase inhibitor (TKI), of 26 months (1)<br>Tumour response rate >30%, compared to standard of care (sutent), of 27% (1) |

| | |
|---|---|
| disease activity by a certain amount.) | |
| 8. In your view, is there an unmet need for patients and healthcare professionals in this condition? | There is absolutely a huge unmet need.<br>With standard of care, sutent, >95% of patients will progress on first line treatment, usually within the first 6 months to 2 years. The chance of long-term control is rare. There is a need for a treatment offering the chance of long-term control.<br>Side effects are universal with sutent, effecting quality of life in most patients. There is a need for a treatment with minimal effect on quality of life. |
| **What is the expected place of the technology in current practice?** | |
| 9. How is the condition currently treated in the NHS? | Currently, fit patients <80 with no significant autoimmune disease and intermediate or poor IMDC risk renal cancer (International Metastatic Database Consortium) are offered ipilimumab nivolumab funded by the cancer drug fund (cdf). Good risk patients, and patients not fit for ipilimumb nivolumab are offered single agent TKI, often sutent, or tivozanib funded by the cdf.<br>In Scotland, combination of TKI (axitinib) with immunotherapy (pembrolizumab) is being used in some patients (2). In England, axitinib avelumab is used in some centres for some patients (3), funded by the cdf |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | ESMO guidelines 2020 (4) |

| | |
|---|---|
| • 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 recommended ESMO pathway is given below.<br><br>However, funding is not available in the UK for cabozantanib nivolumab. Axitinib pembrolizumab is not funded by the cdf although is available in Scotland.<br>Some professionals have less experience with ipilimumab nivolumab combination and prefer single agent TKI (sutent, tivozanib), or combination axitinib avelumab |

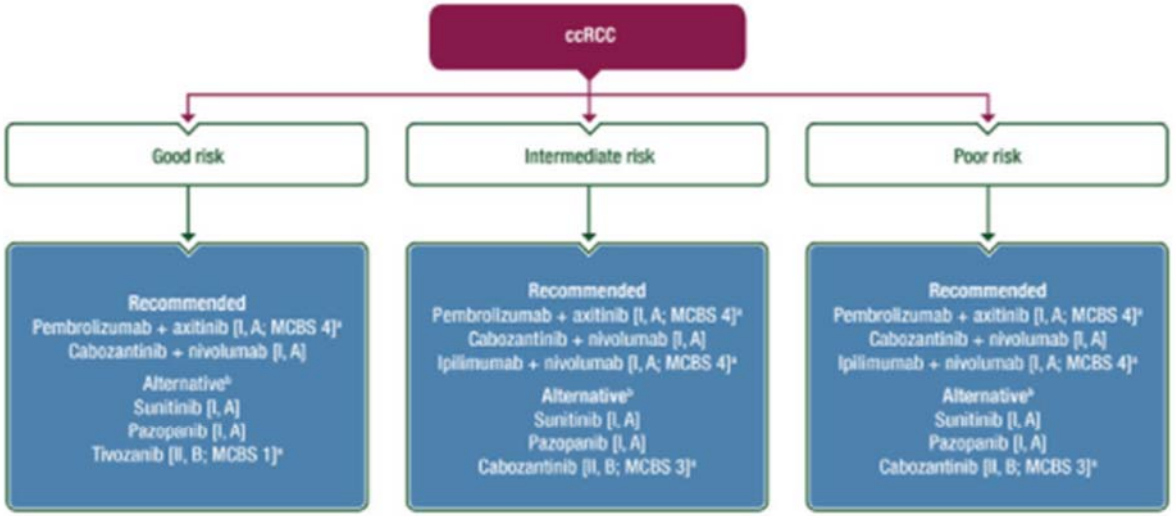


Figure 1. Systemic first-line treatment of clear cell renal cell carcinoma (ccRCC)

a. ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

b. Where recommended treatment not available or contraindicated.
ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; MCBS, Magnitude of Clinical Benefit Scale.

| | |
|---|---|
| • Has current standard care changed since the | Yes<br>Please see above ESMO guidelines 2020 |

| | |
|---|---|
| publication of the guidance in March 2019? (it lists pazopanib, sunitinib, tivozanib and cabozantinib as standard care for intermediate- or poor-risk advanced renal cell carcinoma) | |
| 10. The previous guidance noted that prognostic risk scores such as International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score and the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score are not routinely used in UK clinical practice. Has this changed since TA581 was published? | The risk score needs to be calculated to authorise a prescription for ipilimumab nivolumab and to guide decision about which single agent TKI to use<br>Most centres therefore would now use a risk score<br>IMDC is used in preference as this was used in the original trial of iplilimumab nivolumab (1), although both scores are used |

| | |
|---|---|
| Is one preferred over the other and, if so, why? | |
| 11. Will the technology be used (or is it already used) in the same way as expected care in NHS clinical practice? | The technology is already being used, and funded on the CDF as expected care in suitable fit patients with no significant autoimmune disease and intermediate or poor IMDC risk renal cancer. |
| • How does healthcare resource use differ between the technology and current care? | |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Ipilimumab nivolumab is only given in chemotherapy units in specialist cancer centres/secondary care. |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | No further investment as the training and facilities for the technology have already been established. |

| | |
|---|---|
| 12. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Significant benefits are expected, compared to standard of care sutent<br>Reference to the updated data for ipilimumab nivolumab at 48 months follow up (5)<br>Response rates for ipilimumab nivolumab 42% vs sutent 26.8%<br>Complete response rates 10.4% vs 1.4% |
| • Do you expect the technology to increase length of life more than current care? | Yes, significantly (5)<br>The landmark paper by motzer et al, the initial comparison between ipilimumab and nivolumab (1) showed the following data at median follow up 25.2 months, in intermediate and poor risk patients.<br><br>18-month survival rate with ipilimumab nivolumab 75% (95% CI 70-78), compared with 60% with sutent (95% CI 55-65)<br>Median overall survival for ipilimumab nivolumab not reached versus 26 months for sutent (Hazard ratio for death 0.6 p<0.01)<br>Response rates 42% versus 27 % (p<0.01) (1)<br><br>With extended follow up, median follow up 32.4 months (6),<br>Median overall survival for ipilimumab nivolumab not reached versus 26.6 months for sutent (Hazard ratio for death 0.66 (95% CI 0·54–0·80, p<0·0001)<br>Response rates 42% versus 29 % (p=0.0001)<br><br>At 42 months, 52% of patients treated with ipi/nivo were still alive versus 39% with sutent (HR for median OS 0.66, 95% CI, 0.55-0.80) (7)<br>At 42m, 33% of patients were free of progression (vs 16% with sunitinib) demonstrating potential for long term durable disease control<br>Latest data analysis minimum 48 month follow up in intermediate and poor risk patients:<br>Median Overall survival (OS) sutent =26.6 months<br>Median OS ipilimimab nivolumab=48.1 months |

| | |
|---|---|
| | HR 0.65;(95% CI, 0.54-0.78)<br><br>The shape of the progression free survival curve for ipilimumab nivolumab shows a plateau at 30 months at 35%, suggesting there may be some long term responders.<br><br>There is a marked improvement in complete response rates (>10% vs 1%) which in some may lead to long term control. |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes<br>Ipilimumab nivolumab led to fewer symptoms and better health related quality of life (HRQoL) than sutent, with reduction in deterioration of several HRQoL scores including FKSI-19 total score (HR 0.54 95% CI 0.46-0.63) and FACT-G score (0.63, 0.52-0.75) (8) |
| 13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | Fit patients, performance status 0/1, <80 years old with no significant autoimmune disease and intermediate or poor IMDC risk renal cancer. Evidence for benefit in favourable risk patients is less clear (5)<br>Patients with sarcomatoid histology have a particular benefit:-<br>With 42 months' minimum follow-up, median OS NIVO+IPI for sarcomatoid renal cancer not reached (95%CI 25.2-not estimable *n* = 74] versus sunitinib [14.2 months (9.3-22.9); *n* = 65; HR, 0.45 (95% CI, 0.3-0.7; *P* = 0.0004)]; ORR was 60.8% with NIVO+IPI for sarcomatoid versus 23.1% with sunitinib, with complete response rates of 18.9% versus 3.1%, respectively (9) |
| **The use of the technology** | |
| 14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current | No further practical implications, as the training and facilities for the technology have already been established as the drug combination is being used on the cancer drug fund |

| | |
|---|---|
| care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | Compared to single agent TKI (sutent), the drugs are given intravenously, so do have an impact on chemotherapy nursing/pharmacy workload |
| 15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Patients are imaged with CT every 3 months, or earlier if clinically indicated<br><br>Treatment will be stopped if there is significant progression |
| 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 | Some patients prefer not to take tablets as this is a daily reminder of their condition and prefer an intravenous therapy. |

| | |
|---|---|
| the quality-adjusted life year (QALY) calculation? | |
| 17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | Yes, it offers significant improvement in overall survival, response rates, and complete response rates, with the suggestion of long-term response for some patients, and significant improvement in quality of life, compared to standard of care |
| • 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, see above |
| 18. How do any side effects or adverse effects of the | Quality of life is better than with sutent (8) |

| | |
|---|---|
| technology affect the management of the condition and the patient's quality of life? | The side effects from ipilimumab nivolumab are different to sutent, tend to occur in the first 4-6 months (10), but then mostly resolve , which means that long term quality of life is better. Side effects from sutent are throughout treatment, and often worsen with time |
| **Sources of evidence** | |
| 19. Do the clinical trials on the technology reflect current UK clinical practice? (e.g. in the proportion of people with different levels of prognostic risk) | 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? | Median overall survival, landmark survival, response rates, complete response rate, progression free survival, quality of life<br><br>These were all measured in the trials |

| | |
|---|---|
| • 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 not be found by a systematic review of the trial evidence? | No |
| 21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [Sunitinib: TA169]? Please note, the original scope from [TA581] is being | Pazopanib, tivozanib (11), cabozantanib (12) are all licensed for first line treatment of metastatic renal cancer, as is axitinib avelumab (3) and axitinib pembrolizumab (2)<br><br>Sutent is still widely used and reasonable to be standard of care |

| | |
|---|---|
| used in this review, therefore no additional comparators will be considered. | |
| 22. How do data on real-world experience compare with the trial data? | Real world data compare favourably<br><br>Allison et al reported use of ipilimumab nivolumab in the north west in patients (13)<br><br>Response rates were 45%, complete response 9% with ≥Grade 3 immune related toxicity in 35% |
| **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. | |

| **Second-line treatments** | |
|---|---|
| 24. What second-line treatments are used in clinical practice after sunitinib? What would be expected to be used in clinical practice after nivolumab plus ipilimumab? | Nivolumab or cabozantanib are used second line after sunitinib<br><br>After ipilimumab nivolumab the majority of patients receive cabozantanib with a minority receiving sunitinb or tivozanib or lenvantanib everolimus |

**Key messages**

25. In up to 5 bullet points, please summarise the key messages of your submission.

- Ipilimumab nivolumab offers significant improvement in median overall survival compared to standard of care 48.1 vs 26.6 months at 48 month follow up
- Ipilimumab nivolumab offers significant improvement in response rates 42% vs 26.8% and complete response rates 10.4% vs 1.4% compared to standard of care
- At 42m, 33% of patients were free of progression (vs 16% with sunitinib) demonstrating potential for long term durable disease control
- Quality of life is significantly improved with ipilimumab nivolumab
- Trial data is supported by real world data, supporting this technology as a step change in the treatment of metastatic renal cancer

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID3880]

## Cancer Drugs Fund Review of TA581

This report was commissioned by the NIHR Systematic Reviews Programme as project number 135270

Completed 12 October 2021
Updated 29 October 2021

CONTAINS COMMERCIAL IN CONFIDENCE AND ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

| | |
|---|---|
| **Title:** | Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID3880] (Cancer Drugs Fund Review of TA581) |
| **Produced by:** | Liverpool Reviews & Implementation Group (LR*i*G) |
| **Authors:** | James Mahon, Director, Coldingham Analytical Services, Berwickshire<br><br>Sophie Beale, Director, Hare Research, North Yorkshire<br><br>Angela Boland, Director, LR*i*G, University of Liverpool<br><br>Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool |
| **Correspondence to:** | Angela Boland, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB |
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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 Systematic Reviews Programme. Any errors are the responsibility of the authors



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**Contributions of authors:**

| | |
|---|---|
| James Mahon | Critical appraisal of the economic evidence |
| Sophie Beale | Critical appraisal of the clinical and economic evidence, editorial input |
| Angela Boland | Critical appraisal of the clinical and economic evidence, editorial input |
| Nigel Fleeman | Critical appraisal of the clinical evidence |

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AC | Appraisal Committee |
| CDF | Cancer Drugs Fund |
| CS | Company submission |
| ECOG | Eastern Cooperative Oncology Group |
| ERG | Evidence Review Group |
| ICER | Incremental cost effectiveness ratio |
| IMDC | International Metastatic RCC Database |
| LLN | Lower limit of normal |
| MAA | Managed Access Scheme |
| NICE | National Institute for Health and Care Excellence |
| OS | Overall survival |
| PAS | Patient Access Scheme |
| PFS | Progression-free survival |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality adjusted life years |
| Q2W | Every 2 weeks |
| Q3W | Every 3 weeks |
| Q4W | Every 4 weeks |
| RCC | Renal cell carcinoma |
| SACT | Systemic Anti-Cancer Therapy |
| SmPC | Summary of Product Characteristics |
| ToE | Terms of Engagement |
| ULN | Upper limit of normal |

# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. A summary of the key issues is provided in Section 1.1. There are no clinical effectiveness issues that can be resolved within the timeframe of this Cancer Drugs Fund Review. The cost effectiveness issues identified by the ERG are described in more detail in Section 1.2. Summaries of the company's and the ERG's cost effectiveness results are presented in Section 1.3 and Section 1.4 respectively. Further details about the issues identified by the ERG are provided in the main body of the report.

All the issues outlined in this report represent the views of the ERG; they do not represent the opinion of NICE.

## *1.1 Overview of the ERG's key issues*

Table A Summary of ERG key issues

| ID3880 | Summary of issue | Report sections |
|---|---|---|
| Issue 1 | Company OS model projections | Section 4.1 |
| Issue 2 | Relative proportions of intermediate- and poor-risk patients in the CheckMate 214 trial and the SACT dataset | Section 4.3 |

ERG=Evidence Review Group; OS=overall survival; SACT=Systemic Anti-Cancer Therapy

## *1.2 The cost effectiveness evidence: summary of the ERG's key issues*

Issue 1 Company overall survival model projections

| | |
|---|---|
| **Report section** | 4.1 |
| **Description of issue and why the ERG has identified it as important** | The ERG considers that the company OS model projections for patients who received NIVO+IPI in the first-line setting do not reflect the CheckMate 214 trial 60-month minimum follow-up OS data |
| **What alternative approach has the ERG suggested?** | The ERG has adjusted the company base case OS model projections so that they are more in line with CheckMate 214 trial OS data |
| **What is the expected effect on the cost-effectiveness estimates?** | The effect of the ERG changes is to increase the company base case cost effectiveness results |
| **What additional evidence or analyses might help to resolve this key issue?** | None |

ERG=Evidence Review Group; OS=overall survival

Issue 2 Fewer poor-risk patients in the CheckMate 214 trial than in the SACT dataset

| | |
|---|---|
| **Report section** | 4.3 |
| **Description of issue and why the ERG has identified it as important** | There are fewer poor-risk patients in the CheckMate 214 trial than in the SACT dataset (21% and 35% respectively). If the NICE Appraisal Committee considers that this difference means that the CheckMate 214 trial results are not generalisable to the NHS, then the cost effectiveness results presented by the company and the ERG are unlikely to be generalisable to the NHS |
| **What alternative approach has the ERG suggested?** | None |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown |
| **What additional evidence or analyses might help to resolve this key issue?** | If the NICE Appraisal Committee considers that the CheckMate 214 trial results are not generalisable to the NHS, then further analyses by risk status will be required |

ERG=Evidence Review Group; NHS=National Health Service; SACT=Systemic Anti-Cancer Therapy

## *1.3 Company cost effectiveness results*

Key company cost effectiveness results are presented in Table A (nivolumab+ipilimumab [NIVO+IPI] versus sunitinib) and Table B (NIVO+IPI versus pazopanib).

Table A Company model base case results for the comparison of NIVO+IPI versus sunitinib (PAS prices for nivolumab, ipilimumab and sunitinib)

| Technologies | Total | | | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|---|---|---|
| | Costs | LYG | QALYs | Costs | LYG | QALYs | |
| **Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry** | | | | | | | |
| NIVO+IPI | [redacted] | 7.93 | 4.40 | - | - | - | - |
| Sunitinib | [redacted] | 5.05 | 2.99 | £41,375 | 2.88 | 1.41 | £29,410 |
| **Cost effectiveness analysis 3: New company base case (corrections from FAD model and updated PAS) with 60-month CheckMate 214 trial data** | | | | | | | |
| NIVO+IPI | [redacted] | 8.08 | 4.62 | - | - | - | - |
| Sunitinib | [redacted] | 5.35 | 3.13 | £38,451 | 2.73 | 1.49 | £25,827 |

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: CDF Review CS, Table 15

Table B Company model base case results for the comparison of NIVO+IPI versus pazopanib (PAS prices for nivolumab, ipilimumab and pazopanib)

| Technologies | Total | | | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|---|---|---|
| | Costs | LYG | QALYs | Costs | LYG | QALYs | |
| **Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry** | | | | | | | |
| NIVO+IPI | [redacted] | 7.93 | 4.40 | - | - | - | - |
| Pazopanib | [redacted] | 5.05 | 2.99 | £39,449 | 2.88 | 1.41 | £28,042 |
| **Cost effectiveness analysis 3: New company base case (corrections from FAD model and updated PAS) with 60-month CheckMate 214 trial data** | | | | | | | |
| NIVO+IPI | [redacted] | 8.08 | 4.62 | - | - | - | - |
| Pazopanib | [redacted] | 5.35 | 3.13 | £36,540 | 2.73 | 1.49 | £24,543 |

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: CDF Review CS, Table 15

### *1.4 ERG scenario analyses results*

The ERG has adjusted the company OS model projections so that they are more in line with CheckMate 214 trial data. Two scenarios have been carried out. In scenario analysis 1, NIVO+IPI mortality hazards are set equal to the mortality hazards of the comparator treatment from month 54 onwards. In scenario analysis 2, mortality hazards for the comparator treatment are set equal to mortality hazards for NIVO+IPI from month 54 onwards. Results from the two scenario analyses for the comparison of NIVO+IPI versus sunitinib are displayed in Table C and results from the two scenario analyses for the comparison of NIVO+IPI versus pazopanib are displayed in Table D.

Table C ERG Scenario analysis results for the comparison of NIVO+IPI versus sunitinib (PAS prices for nivolumab, ipilimumab and sunitinib)

| Technologies | Total | | | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|---|---|---|
| | Costs | LYG | QALYs | Costs | LYG | QALYs | |
| **Scenario 1: mortality hazards for NIVO+IPI set equal to mortality hazards for sunitinib from month 54 onwards** | | | | | | | |
| NIVO+IPI | [redacted] | 6.896 | 4.132 | - | - | - | - |
| Sunitinib | [redacted] | 5.349 | 3.131 | £36,082 | 1.547 | 1.001 | £36,041 |
| **Scenario 2: mortality hazards for sunitinib set equal to mortality hazards for NIVO+IPI from month 54 onwards** | | | | | | | |
| NIVO+IPI | [redacted] | 8.083 | 4.620 | - | - | - | - |
| Sunitinib | [redacted] | 6.199 | 3.474 | £36,735 | 1.885 | 1.145 | £32,073 |

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: ERG adjusted company model

Table D ERG Scenario analysis results for the comparison of NIVO+IPI versus pazopanib (PAS prices for nivolumab, ipilimumab and pazopanib)

| Technologies | Total | | | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|---|---|---|
| | Costs | LYG | QALYs | Costs | LYG | QALYs | |
| **Scenario 1: mortality hazards for NIVO+IPI set equal to mortality hazards for pazopanib from month 54 onwards** | | | | | | | |
| NIVO+IPI | [redacted] | 6.896 | 4.132 | - | - | - | - |
| Pazopanib | [redacted] | 5.349 | 3.131 | £34,170 | 1.574 | 1.001 | £34,132 |
| **Scenario 2: mortality hazards for pazopanib set equal mortality hazards for to NIVO+IPI from month 54 onwards** | | | | | | | |
| NIVO+IPI | [redacted] | 8.083 | 4.620 | - | - | - | - |
| Pazopanib | [redacted] | 6.199 | 3.474 | £34,824 | 1.885 | 1.145 | £30,404 |

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: ERG adjusted company model

# 2 BACKGROUND

## *2.1 Introduction*

In May 2019, the National Institute for Health and Care Excellence (NICE) recommended nivolumab with ipilimumab (NIVO+IPI),[1] within the Cancer Drugs Fund (CDF), as an option for adults with untreated advanced renal cell carcinoma (RCC) that is intermediate- or poor-risk as defined by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, if the conditions set out in the Managed Access Agreement (MAA)[2] for NIVO+IPI were followed.

This CDF Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE[3]) document issued by NICE. The ToE,[3] although not binding, outline NICE's expectations relating to the content of the CDF Review company submission (CS) for the CDF review.

## *2.2 Nivolumab+ipilimumab*

Key facts (CDF Review CS, Table 2):

- European Marketing Authorisation,[4] issued in January 2019, permitted NIVO+IPI to be used in combination to treat untreated, advanced RCC in adults with intermediate- or poor-risk disease
- the drugs are administered via intravenous infusion: NIVO 3mg/kg plus IPI 1mg/kg Q3W for four doses, followed by NIVO 240mg Q2W or 480mg Q4W. Treatment is continued as long as clinical benefit is observed or until the patient no longer tolerates treatment
- no diagnostic test is required for this indication
- nivolumab and ipilimumab are available to the NHS at (confidential) discounted prices via Patient Access Schemes (PAS).

## *2.3 Evidence sources*

The two main sources of evidence for this review are the CheckMate 214 trial[5] (primary source) and the Systemic Anti-Cancer Therapy (SACT) data[6] (secondary source). The company considers that data from the latest data-cut of the CheckMate 214 trial provides sufficient evidence to address the NICE Appraisal Committee's main uncertainties (as detailed in the Data Collection Agreement[2]).

### 2.3.1 CheckMate 214 trial

The company's main source of clinical effectiveness evidence for this appraisal is the CheckMate 214 trial. This is a phase III, randomised, open-label study of NIVO+IPI versus sunitinib monotherapy in patients with previously untreated advanced RCC with a clear-cell component. The trial was conducted in 184 sites in 28 countries, including six sites in the UK, of which four were in England (initial CS, p16). To be eligible for the intermediate-/poor-risk

cohort, at least one of the six prognostic factors as per the IMDC criteria had to be present. The prognostic factors (initial CS, Table 3) are:

- time from diagnosis to systemic treatment<1 year
- haemoglobin <lower limit of normal (LLN) (13.5 to 17.5 g/dL for men and 12.0 to 15.5 g/dL for women)
- corrected calcium concentration >10mg/dL
- Karnofsky Performance Status <80%
- absolute neutrophil count >upper limit of normal (ULN)
- platelet count >ULN.

The trial design is shown in Figure 1.

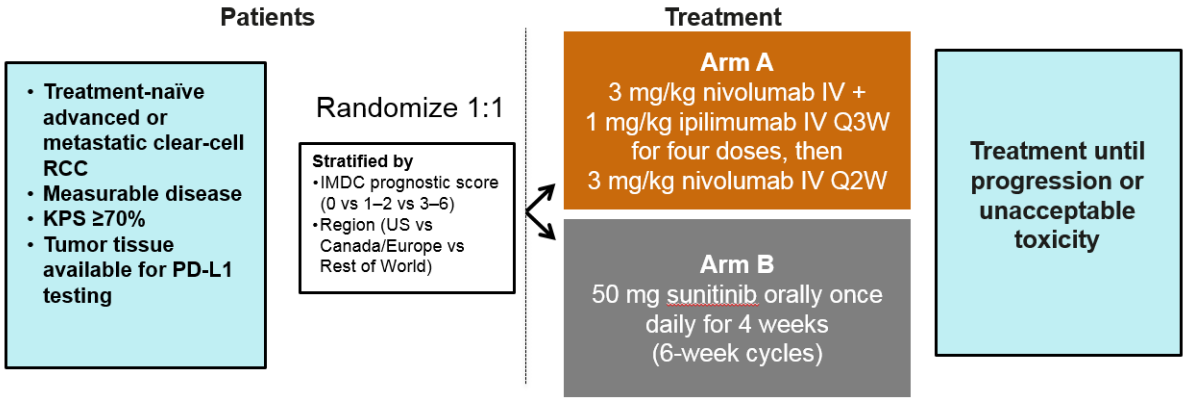


Figure 1 CheckMate 214 trial diagram

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IV=intravenous; KPS=Karnofsky Performance Score; PD-L1=programmed death-ligand 1; Q2W=every 2 weeks; Q3W=every 3 weeks; RCC=renal cell carcinoma
Source: Escudier 2017[7]

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 permitted treatment crossover from the sunitinib arm to the NIVO+IPI arm.

The survival data used to inform the CDF Review CS are 60-month minimum follow-up CheckMate 214 trial data from February 2021; these data provide 30 more months of follow-up data than were available at the time of the initial appraisal (CDF Review CS, p16).

**CheckMate 214 trial results**

Key CheckMate 214 trial results are presented in Table 1.

Table 1 Key CheckMate 214 trial results

| Outcome | Treatment | Median, months (95% CI) | HR (95% CI) |
|---|---|---|---|
| **Overall survival** | | | |
| Initial CS (30 month minimum follow up) | NIVO+IPI (n=425) | NA (35.6 to NA) | 0.66 (0.54 to 0.80) |
| | Sunitinib (n=422) | 26.6 (22.1 to 33.4) | |
| CDF Review CS (60 month minimum follow up) | NIVO+IPI (n=425) | 47.0 (35.4 to 57.4) | 0.68 (0.58 to 0.81) |
| | Sunitinib (n=422) | 26.6 (22.1 to 33.5) | |
| **Progression-free survival (IRRC secondary definition)** | | | |
| Initial CS (18 month minimum follow up) | NIVO+IPI (n=425) | [redacted] | [redacted] |
| | Sunitinib (n=422) | [redacted] | |
| CDF Review CS (60 month minimum follow up) | NIVO+IPI (n=425) | [redacted] | [redacted] |
| | Sunitinib (n=422) | [redacted] | |
| **Time to treatment discontinuation** | | | |
| Initial CS (30 month minimum follow up) | NIVO+IPI (n=423) | [redacted] | [redacted] |
| | Sunitinib (n=416) | [redacted] | |
| CDF Review CS (60 month minimum follow up) | NIVO+IPI (n=423) | [redacted] | [redacted] |
| | Sunitinib (n=416) | [redacted] | |
| [redacted] | | | |

CDF=Cancer Drugs Fund; CI=confidence interval; CS=company submission; HR=hazard ratio; IRCC=Independent Radiology Review Committee; NA=not applicable
Source: CDF Review CS (Table 6, Table 8 and Table 10)

### 2.3.2 SACT data

Public Health England (PHE) provided a report for this appraisal. This report includes results from analyses of data collected from patients who received NIVO+IPI via the CDF. Applications were received between 4 April 2019 and 30 November 2020, and patients were traced for their vital status on 28 April 2021. Data are available for the 814 patients with a SACT database treatment record for a maximum period of 24 months; minimum OS follow up is 5 months (152 days) and median OS follow up is 10.8 months. Median OS had not been reached. Further OS results are presented in Table 2.

Table 2 SACT overall survival results

| Time point | Patients alive % (95% CI) |
|---|---|
| 6 months | 80% (95% CI: 77% to 83%) |
| 12 months | 69% (95% CI: 65% to 72%) |
| 18 months | 61% (95% CI: 57% to 64%) |

Source: SACT report,[6] p26

# 3 THE CLINICAL DECISION PROBLEM

The NICE Appraisal Committee's preferred clinical assumptions (as set out in the ToE[3]) are presented in Table 3. Further information relating to each assumption is provided in the text following the table.

Table 3 ERG summary of NICE AC preferred clinical assumptions

| Area | ERG summary of NICE Appraisal Committee's preferred assumptions |
|---|---|
| Population | Adults with intermediate- or poor-risk untreated advanced RCC are the relevant population. Data collected through SACT should be used to inform the proportion of people with intermediate- and poor-risk disease |
| Comparators | The company should present clinical and cost effectiveness evidence for NIVO+IPI versus sunitinib and versus pazopanib |
| PFS definition | PFS secondary definition (IRRC assessed, no censoring on receipt of subsequent therapy) should be used to inform NICE AC decision-making |
| Subsequent treatments | The company should explore the most appropriate modelling of subsequent treatments, supported by data collected through SACT |

AC=Appraisal Committee; ERG=Evidence Review Group; IRRC=Independent Radiological Review Committee; PFS=progression-free survival; RCC= renal cell carcinoma; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2021[3]

## *3.1 Population*

Box 1 NICE Appraisal Committee's preferred assumption: population

| NICE-preferred assumption | ERG comment |
|---|---|
| Adults with intermediate- or poor-risk untreated advanced or metastatic RCC | The company has provided appropriate data for the relevant population |

ERG=Evidence Review Group
Source: NICE 2021[3]

The population described in the final scope[8] issued by NICE is people with untreated intermediate- or poor-risk (as per IDMC criteria) advanced or metastatic RCC. The key trial providing evidence to support this appraisal, the CheckMate 214 trial, enrolled patients with untreated advanced or metastatic RCC with any level of risk (favourable, intermediate or poor). All results presented in this ERG report relate only to the intermediate- and poor-risk group.

**Comparison of CheckMate 214 and SACT populations**

The company suggested (CDF Review CS, p31 and Appendix A.15.9) that the characteristics of patients included in the SACT dataset[6] are likely to have been impacted by COVID-19. Specifically, the company suggested that COVID-19 was likely to have resulted in sicker patients being included in the SACT dataset[6] and poorer treatment outcomes (CS, Appendix A.15.9); however, evidence provided by the company[9,10] to support this conclusion is limited.

Clinical advice to the company is that the baseline characteristics of the SACT cohort are more representative of the patients they see in NHS clinical practice than the patients enrolled in the CheckMate 214 trial. Compared with SACT data,[6] the CheckMate 214 trial population

comprises a lower proportion of patients with poor-risk disease (21% versus 35%), and a higher proportion of patients with intermediate-risk disease (79% versus 65%), as shown in Table 4.

Table 4 Patient baseline characteristics: CheckMate 214 trial and SACT database

| Baseline characteristic | CheckMate 214* | | SACT dataset N=814 | |
|---|---|---|---|---|
| | NIVO+IPI N=425 | Sunitinib N=422 | | |
| **Sex** | | | | |
| Male | 314 (74%) | 301 (71%) | 596 (73%) | |
| Female | 108 (25%) | 121 (29%) | 218 (27%) | |
| **Age (years)** | | | | |
| | Median (range) | | | |
| | 62 (26 to 85) | 61 (21 to 85) | 61 (NA)<br>Male: 60 (NA)<br>Female: 63 (NA) | |
| **Performance status** | | | | |
| KPS 100% | [redacted] | [redacted] | ECOG PS 0 | 285 (35%) |
| KPS 90% | [redacted] | [redacted] | ECOG PS 1 | 420 (52%) |
| KPS 80% | [redacted] | [redacted] | ECOG PS 2 | 41 (5%) |
| KPS 70% | [redacted] | [redacted] | ECOG PS 3 | 1 (<1%) |
| KPS <70% | [redacted] | [redacted] | ECOG PS 4 | 0 (0%) |
| Missing | - | - | Missing | 67 (8%) |
| **IMDC disease risk** | | | | |
| Intermediate risk (IMDC score 1 or 2) | 79% | 79% | 533 (65%) | |
| Poor risk (IMDC score 3 to 6) | 21% | 21% | 281 (35%) | |

*Intermediate- and poor-risk patients
ECOG PS=Eastern Co-operative Oncology Group Performance Status; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; KPS=Karnofsky Performance Status; NA=not available; SACT=Systemic Anti-Cancer Therapy
Source: Initial CS (Table 6) and SACT report[6] (Table 4 and Table 5)

Proportions of patient populations with poor-risk disease are available from five[5,6,11-13] studies identified by the company (CDF Review CS, Section A.6.2.1) (Table 5). These data show that the proportion of patients in the SACT dataset[6] with poor-risk disease is higher than the proportions of patients with poor-risk disease in the other four studies.[5,6,11-13] Clinical advice to the ERG at the time of the initial appraisal (ERG report, p39) was that in NHS clinical practice, approximately 30% of patients have poor-risk disease. This estimate is 5% lower than the proportion in the SACT dataset[6] and 2% higher than the proportion in the real-world study (28%).[11]

The company highlighted (CDF Review CS, p30) that the issue of the proportion of patients with poor-risk disease was not considered an area of uncertainty in either the NICE appraisal of pembrolizumab+axitinib[14] or the NICE appraisal of avelumab+axitinib.[15]

The ERG considers that the relative proportions of patients with intermediate- and poor-risk disease are only important if the costs and outcomes associated with treating these two groups of patients differ. This issue is discussed further in Section 4.3.

Table 5 Proportions of patients with poor-risk disease (IMDC score 3 to 6)

| Study identity | Proportion of patients with poor-risk disease | |
|---|---|---|
| CheckMate 214 trial | NIVO+IPI: 21% | |
| SACT database[6] | NIVO+IPI: 35% | |
| KEYNOTE 426[12] trial | Pembrolizumab+axitinib:19% | Sunitinib: 17% |
| JAVELIN Renal 101[13] trial | Avelumab+axitinib: 21% | Sunitinib: 20% |
| Real-world data[11] | 28% | |

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium

## *3.2 Comparators*

Box 2 Appraisal Committee's preferred assumption: comparators

| NICE-preferred assumption | ERG comment |
|---|---|
| The company should present clinical and cost effectiveness evidence for NIVO+IPI versus sunitinib and versus pazopanib | The company has provided appropriate data for the relevant comparators. The efficacy of pazopanib has been assumed to be the same as the efficacy of sunitinib |

ERG=Evidence Review Group
Source: NICE 2021[3]

Both sunitinib and pazopanib are available to NHS patients only if the treatments are made available in accordance with their respective Patient Access Scheme (PAS) agreements.

Relevant marketing indications and NICE guidance for the comparator treatments listed in the final scope issued by NICE are provided in Table 6.

Table 6 Marketing indication and NICE guidance: comparator treatments

| Agent | Marketing indication (in relation to RCC) | NICE guidance (in relation to RCC) |
|---|---|---|
| Sunitinib (Sutent) | SUTENT is indicated for the treatment of advanced/metastatic RCC in adults[16] | **First-line (TA169, 25 March 2009[17]):** Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1 |
| Pazopanib (Votrient) | Votrient is indicated in adults for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease[18] | **First-line (TA215, 23 February 2011[19]):** Pazopanib is recommended as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an ECOG PS of 0 or 1<br>**Second-line, ID70 (2010):** No guidance issued (topic discontinued 14 April 2010) |

ECOG=Eastern Cooperative Oncology Group; PAS=Patient Access Scheme; PS=performance status; RCC=renal cell carcinoma
Sources: Marketing indications taken from the summary of product characteristics documents available on the European Medicines Agency website and NICE guidance taken from the NICE website

The ERG highlights that since NIVO+IPI entered the CDF the following first-line treatments have been recommended by NICE:

- tivozanib has been recommended by NICE as a treatment option for adults with untreated advanced RCC (TA512[20])
- cabozantinib has been recommended by NICE as a treatment option for adults with untreated advanced RCC that is intermediate- or poor-risk as defined by the IMDC criteria (TA542[21])
- avelumab+axitinib has been recommended for use within the CDF as an option for untreated advanced RCC (TA645[15]).

The ERG highlights that cabozantinib and tivozanib have been demonstrated to be cost effective versus sunitinib and versus pazopanib (and that avelumab+axitinib has also been compared with sunitinib and pazopanib). In addition, treatment with lenvatinib+pembrolizumab is currently being appraised by NICE, as a Multiple Technology Appraisal (MTA), for adults with untreated advanced RCC (ID3760[22]). The comparators in this MTA for the whole at-risk population are sunitinib, pazopanib and tivozanib, whilst the comparators for the intermediate- and poor-risk population are sunitinib, pazopanib, tivozanib, cabozantinib and NIVO+IPI (if the latter is recommended by NICE before the end of the MTA).

### *3.3 Progression-free survival data*

Box 3 NICE Appraisal Committee's preferred assumption: PFS definition

| NICE-preferred assumption | ERG comment |
|---|---|
| PFS secondary definition (IRRC assessed, no censoring on receipt of subsequent therapy) should be used to inform NICE AC decision-making | The company has provided the requested PFS analysis results. Summary results are provided in Table 1 |

AC=Appraisal Committee; ERG=Evidence Review Group; IRRC=Independent Radiological Review Committee
Source: NICE 2021[3]

### *3.4 Subsequent treatments*

Box 4 NICE Appraisal Committee's preferred assumption: subsequent treatments

| NICE-preferred assumption | ERG comment |
|---|---|
| The company should explore the most appropriate modelling of subsequent treatments, supported by data collected through SACT | None of the treatments received by SACT dataset patients have been recommended by NICE as second-line treatments following immunotherapy |

ERG=Evidence Review Group; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2021[3]

The data presented in Table 7 and Table 8 show the subsequent treatments received by patients whose first-line treatment was NIVO+IPI (CheckMate 214 trial and SACT dataset respectively).

Table 7 Subsequent treatments received by CheckMate 214 trial patients randomised to receive NIVO+IPI

| Subsequent treatments | 30-month minimum follow up, n (%) [redacted] | 60-month minimum follow up, n (%) [redacted] |
|---|---|---|
| Sunitinib | [redacted] | [redacted] |
| Axitinib | [redacted] | [redacted] |
| Pazopanib | [redacted] | [redacted] |
| Cabozantinib | [redacted] | [redacted] |
| Everolimus | [redacted] | [redacted] |
| Nivolumab | [redacted] | [redacted] |
| Lenvatinib | [redacted] | [redacted] |
| Investigational antineoplastic | [redacted] | [redacted] |

Note: some patients received more than one treatment
Source: CDF Review CS, Table 11

Table 8 First subsequent treatments for SACT dataset patients treated with NIVO+IPI (data available at 24 months, minimum follow up 5 months)

| Subsequent treatments | n=234/814 n (%) | NICE second-line recommendation |
|---|---|---|
| Axitinib | 6 (2.6) | Treatment option for adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine (TA333[23]) |
| Cabozantinib | 139 (59.4) | Treatment option for adults with advanced RCC after VEGF-targeted therapy (TA463[24]) |
| Everolimus | 1 (0.4) | Treatment option for advanced RCC that has progressed during or after treatment with VEGF-targeted therapy (TA432[25]) |
| Tivozanib | 19 (8.1) | - |
| Lenvatinib+everolimus | 5 (2.1) | Treatment option for advanced RCC in adults who have had one previous VEGF-targeted therapy (patients with ECOG PS 0 or 1) (TA498[26]) |
| Sunitinib | 31 (13.2) | No NICE recommendation |
| Pazopanib | 28 (12.0) | No NICE recommendation |
| Dabrafenib+trametinib | 2 (0.9) | No NICE recommendation |
| Carboplatin+pemetrexed | 1 (0.4) | No NICE recommendation |
| Irinotecan+MdG+panitumumab | 1 (0.4) | No NICE recommendation |
| Trial | 1 (0.4) | No NICE recommendation |

Note 1: Some patients received more than one treatment
Note 2: Distribution of further lines of therapy are also available from the SACT report[6] (Table 7)

ECOG PS=Eastern Cooperative Oncology Group Performance Status; MdG=fluorouracil-folic acid; RCC=renal cell carcinoma; TA=technology appraisal; VEGF=vascular endothelial growth factor
Source: SACT report[6]

The ERG considers that a comparison of 30-month minimum follow-up CheckMate 214 trial data and 5-month minimum follow-up SACT[6] data (Table 7 and Table 8) shows that the subsequent treatments received by patients enrolled in the NIVO+IPI arm of the CheckMate 214 trial do not match the subsequent treatments received by the patients who received NIVO+IPI in the NHS:

- half of the patients in the CheckMate 214 trial who received any subsequent treatment were prescribed sunitinib (the comparator treatment); only 13% of the SACT[6] cohort who received a (first) subsequent treatment received sunitinib, 59.4% received cabozantinib
- none of the CheckMate 214 trial patients received a combination therapy.

However, a naïve comparison of CheckMate 214 trial and SACT[6] data is not useful as CheckMate 214 trial data relate to all subsequent treatments whereas the SACT[6] data only relate to first subsequent treatment. Further, if NIVO+IPI were to be recommended by NICE, there is only one NICE recommended second-line treatment for this group of patients (i.e., nivolumab is a treatment option for previously treated advanced RCC [TA417[28]]). Given the uncertainty around appropriate treatments, the ERG considers that the company model should be populated with CheckMate 214 trial data as this source provides evidence for the larger population of patients over a longer period of time (this approach was accepted by the NICE Appraisal Committee in 2018).

### *3.5 ERG clinical effectiveness conclusions*

Whilst the company has considered the appropriate comparators, the ERG highlights that tivozanib[20] and cabozantinib[21] are not considered in this CDF review but have been recommended by NICE as treatment options for this population and are currently being considered in an ongoing MTA [ID3760[22]].

The subsequent treatments for NHS patients who would receive NIVO+IPI in the first-line setting (if recommended by NICE) are unclear.

# 4 THE COST EFFECTIVENESS DECISION PROBLEM

The NICE Appraisal Committee's preferred economic assumptions (as set out in the ToE[3] document) are presented in Table 9. Further information relating to each assumption is provided in the text following the table.

Table 9 ERG summary of NICE Appraisal Committee preferred economic assumptions

| Area | ERG Summary of NICE Appraisal Committee's preferred assumptions | Company approach to assumptions | ERG critique of company approach to assumptions if different to Appraisal Committee preference |
|---|---|---|---|
| Treatment switching | In the CheckMate 214 trial, patients could switch from sunitinib to NIVO+IPI after the trial was stopped early for effectiveness. The company should use more mature OS data from the CheckMate 214 trial to inform the most appropriate approach to treatment switching | The company has not adjusted for treatment switching as the number of patients switching treatment was low | Only [redacted] % of patients in the sunitinib arm of the CheckMate 214 trial switched to NIVO+IPI. The ERG is satisfied that an adjustment for treatment switching is not required and highlights that cost effectiveness results generated based on unadjusted OS K-M data are likely to favour the comparator treatments compared with results generated using data that had been adjusted for treatment switching |
| Extrapolating OS data | The company should use OS data from CheckMate 214 trial to inform the economic model | The company has used updated OS data from the CheckMate 214 trial to generate OS projections | The ERG has concerns about the reliability of the company OS projections (Section 4.1) |
| Immunological effect | The company should use more mature data from the CheckMate 214 trial to inform assumptions about the immunological response | The company has not incorporated an explicit immunological effect | The ERG considers that the company approach was appropriate |
| Stopping rules | The company should not include a stopping rule | The company has not included a stopping rule | The ERG considers that the company approach was appropriate |
| Dosing regimen | The company should use the flat rate dosing regimen for nivolumab | The company has stated that they have used flat based dosing to cost nivolumab in the company model | In the company base case analysis, weight-based dosing is used to estimate the cost of NIVO+IPI (Weeks 1 to 12) and the flat-based dose is used to estimate treatment with nivolumab thereafter. This is in line with the licensed dosing for NIVO+IPI for RCC and is therefore appropriate |

| Area | ERG Summary of NICE Appraisal Committee's preferred assumptions | Company approach to assumptions | ERG critique of company approach to assumptions if different to Appraisal Committee preference |
|---|---|---|---|
| Quality of life | The company should use more mature quality of life data from the CheckMate 214 trial and ensure that it reflects differences by treatment arm, whether the person is on treatment, and disease progression status | The company has carried out a regression analysis using more mature CheckMate 214 trial data to estimate utility values by treatment and health state | The ERG has no major concerns about the utility values used in the company base case analysis (Section 4.2) |
| Subsequent treatments | The company should explore using the CheckMate 214 trial data and SACT data to select the most appropriate methods to estimate subsequent treatments | The company has used subsequent treatments from the CheckMate 214 trial in the base case with subsequent treatments in SACT as a scenario analysis | Given the uncertainty around future second-line treatment options for patients with advanced RCC, the ERG agrees with the company that the CheckMate 214 trial is the most appropriate source of information and is satisfied with the company approach |
| NICE End of Life criteria | The Appraisal Committee considered that NIVO+IPI, for this indication, does not meet the NICE End of Life criteria | The company agrees that NIVO+IPI does not meet the NICE End of Life criteria | The ERG agrees with the company and the Appraisal Committee |

ERG=Evidence Review Group; K-M=Kaplan-Meier; OS=overall survival; RCC=renal cell carcinoma; SACT=Systemic Anti-Cancer Therapy
Source: NICE 2021[3]

The company has submitted an updated version of the company model used to inform the initial appraisal of NIVO+IPI versus sunitinib or pazopanib for untreated advanced RCC. The ERG is satisfied that the structure of the company model is appropriate; however, the ERG has concerns about:

- the validity of company model OS projections
- use of differential utility values by treatment arm
- the impact of the proportion of intermediate- and poor-risk patients being different for patients treated by the NHS compared to in the CheckMate 214 trial.

## *4.1 Overall survival estimates*

In the company base case, compared with patients treated with sunitinib, [redacted]% of the OS gain (and [redacted]% of the quality adjusted life year [QALY] gain) for patients treated with NIVO+IPI occurs during the period between 61 months and the end of the model time horizon (480 months), i.e., the period during which only incomplete CheckMate 214 trial OS data are available. The plausibility of model OS projections is therefore the ERG's main concern.

### 4.1.1 Company methods for overall survival curve selection

The company has followed the methods described in the NICE Decision Support Unit (DSU) Technical Support Document[29] for selecting parametric distributions to model OS using the 60-month minimum follow-up CheckMate 214 trial K-M data. The ERG is satisfied that these methods have been followed appropriately. However, the ERG highlights that the OS predictions for patients treated with NIVO+IPI and sunitinib made by the company and ERG at the time of the initial appraisal (using 30-month minimum follow-up CheckMate 214 trial data) were both overly pessimistic (CDF Review CS, p34). This shows that methods of distribution selection for model parameters such as OS, even when correctly applied, can result in inaccurate projections.

### 4.1.2 Plausibility of company long-term overall survival projections

Review of the company model shows that log-normal distributions were chosen by the company to represent the OS experience of patients randomised to receive NIVO+IPI and sunitinib. These have the following long-term characteristics:

[redacted]

[redacted]

In the company model, patients in the NIVO+IPI arm are modelled to have a lower mortality hazard for 21 years compared to patients in the sunitinib arm; this is not supported by the CheckMate 214 trial annual mortality rates (Table 10) or by the data provided by the company in response to clarification question B2 (reproduced in Figure 2).

Table 10 CheckMate 214 trial annual mortality rates

| Year | NIVO+IPI | Sunitinib |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |
| 6* | [redacted] | [redacted] |

* CheckMate 214 trial data provided in the company model
Source: ERG calculated rates using data from CDF Review CS, Table 5

[redacted]

Figure 2 CheckMate 214 trial OS hazard plots for the 48-month and 60-month minimum follow-up data cuts, plotted up to 48-months (left) and up to 60 months (right)
Source: Company clarification response, Figure 2

Clinical advice to the company was that mortality rates for patients with advanced RCC would decline over time. However, CheckMate 214 trial data suggest that this may be more likely for patients treated with sunitinib compared with patients treated with NIVO+IPI (see Table 10). Whilst evidence from the CheckMate 214 trial beyond Year 5 is limited due to censoring, the annual mortality rate (calculated from the CheckMate 214 trial OS K-M data presented in the

company CDF Review model) in Year 6 of the trial for the NIVO+IPI arm was [redacted]% and that for the sunitinib arm was [redacted]%. Due to censoring, it is unclear whether these data indicate that the mortality rate in the NIVO+IPI arm was substantially higher than that for sunitinib in Year 6. However, Year 6 data do not support a conclusion that the NIVO+IPI arm mortality rate is lower than the sunitinib arm rate.

If mortality rates are increasing over time for the NIVO+IPI arm, or the mortality rate for the NIVO+IPI arm is **not** always lower than the mortality rate for the sunitinib arm, this casts doubt on the long-term OS estimates for the NIVO+IPI arm generated by the log-normal distribution used in the company base case analysis.

The ERG asked the company to provide justification for modelling lower (rather than higher or at least equivalent) mortality rates beyond Year 4 for patients in the NIVO+IPI arm compared with patients in the sunitinib arm (clarification question B1). The justifications provided by the company were that, in the CheckMate 214 trial, patients in the NIVO+IPI arm:

- received different subsequent treatments from patients in the sunitinib arm
- experienced sustained survival benefit (OS, progression-free survival [PFS] and duration of response).

In the CheckMate 214 trial, [redacted] % of patients in the sunitinib arm who received any subsequent treatment received nivolumab, whilst [redacted]% of patients in the NIVO+IPI who received any subsequent treatment received sunitinib. Therefore, if NIVO+IPI is more effective in terms of extending OS than sunitinib, the subsequent treatments received by patients enrolled in the CheckMate 214 trial would not support modelling lower mortality rates in the NIVO+IPI arm of the model than in the sunitinib arm of the model beyond Year 4. Conversely, superior effectiveness, in terms of OS, of NIVO+IPI versus sunitinib would support modelling equal hazards in both arms, or for mortality rates in the NIVO+IPI arm being higher than in the sunitinib arm beyond Year 4. The ERG does not dispute that CheckMate 214 trial data show that 5-year survival, PFS and duration of response are higher for patients in the NIVO+IPI arm compared to patients in the sunitinib arm. However, this evidence is not justification to support modelling mortality hazards for the NIVO+IPI arm that are lower than the mortality hazards for the sunitinib arms after 4 years.

The company also stated in their clarification response that any observed trends between months 48 and 60 should be treated with caution as:

> "*the* [redacted] *in the 60-month data is likely to be* [redacted] (company clarification response to question B1).

However, as a minimum of 60 months follow-up data are available from the CheckMate 214 trial, there is no censoring before Month 60 and so the unsmoothed hazard rates between Month 48 and Month 60 are completely unaffected by censoring.

The options open to the ERG to provide alternative and plausible long-term OS projections are limited. However, given that the 60-month CheckMate trial OS K-M data show that the mortality hazards for the NIVO+IPI arm during Year 5 appear to be (at best) the same as for the sunitinib arm, the ERG has adjusted the company model mortality hazards for the NIVO+IPI arm to equal the mortality hazards for the sunitinib arm from Month 54 (i.e., halfway between Years 4 and Year 5). As it is not clear whether the mortality hazards for the model NIVO+IPI arm should be set equal to the sunitinib arm or vice versa, the ERG has carried out a second scenario in which the mortality hazards for the sunitinib arm are set equal to the mortality hazards for the NIVO+IPI arm at Month 54.

### *4.2 Utility values*

The company has applied differential utilities by treatment arm, for patients on and off treatment and by progression states (progression-free or progressed). Patients in the NIVO+IPI arm have higher values than patients in the sunitinib arm in all cases. The ERG accepts that different utilities by treatment arm is an approach supported by the results of the company's regression analysis of CheckMate 214 trial EQ-5D data. However, application of differential utilities by treatment arm many years after patients are no longer receiving the randomised treatment (and beyond the period for which the company has evidence from the CheckMate 214 trial) has not been justified by the company.

If utility values in all health states for patients treated with NIVO+IPI and sunitinib were equal from the start of the model time horizon (which the ERG would not support), the company's base case incremental cost effectiveness ratio (ICER) per QALY gained for the comparison of NIVO+IPI versus sunitinib would increase by approximately £1,300. The ERG has no evidence to suggest when utility values might equalise and so has not adjusted the company base case; however, if the ERG assumption that equalisation of utility values would happen at some point (in the longer term, after patients stop receiving their first-line treatment) holds, then the company base case ICER would be an overestimate but by no more than £1,300 per QALY gained.

### *4.3 Ratio of intermediate- to poor-risk patients*

It is stated in the ToE[3] that, on exit from the CDF, the NICE Appraisal Committee expects to review an analysis based on the ratio of intermediate- to poor-risk patients in the SACT[6] cohort and how results from this analysis compare with an analysis based on the ratio of intermediate- to poor-risk patients in the CheckMate 214 trial. An analysis shows that the SACT[6] cohort includes 35% poor-risk patients compared to 21% poor-risk patients in the CheckMate 214 trial. The company, whilst accepting that the percentage of poor-risk patients treated with NIVO+IPI would be higher in the NHS than in the CheckMate 214 trial, stated COVID 19 is likely to have resulted in sicker patients being included in the SACT[6] dataset and poorer patient outcomes (CDF Review CS, p31 and Appendix A.15.9). Whether this is a valid reason is unclear; however, it should be noted that 92.3% of SACT[6] dataset patients had an ECOG PS of 0 or 1 (5% had an ECOG PS of 2, <1% had an ECOG PS of 3 and scores were missing for 8% of the group), suggesting that there was no focus on only treating the sickest patients. The ERG considers that the SACT[6] dataset may be a fair reflection of the ratio between intermediate- and poor-risk patients who would be treated with NIVO+IPI in the NHS.

Any difference in the ratio of intermediate- to poor-risk patients who would be treated with NIVO+IPI in the NHS and those enrolled in the CheckMate 214 trial only matters if there are differential outcomes and costs for these two groups of patients. The ERG asked the company to provide CheckMate 214 trial OS, PFS and TTD K-M data separately for intermediate- and poor-risk groups so that it could be determined whether outcomes and costs for these two groups differed (clarification question B3). The company did not provide this information, stating that the CheckMate 214 trial was not powered for analyses of intermediate- and poor-risk patients separately, and the licensed indication is for the pooled population. However, the SACT data suggest OS and treatment duration are lower for the poor-risk than for the intermediate-risk group (Table 11 and Table 12); the cost effectiveness of treatment with NIVO+IPI versus sunitinib may be different for the intermediate- and poor-risk groups.

If the NICE Appraisal Committee considers that the difference in proportions of poor-risk patients in the CheckMate 214 trial and the SACT dataset means that the CheckMate 214 trial results are not generalisable to the NHS, then the cost effectiveness results presented by the company and the ERG are unlikely to be generalisable to the NHS.

Table 11 SACT dataset overall survival data

| Time period | Intermediate risk disease (IMDC score of 1 or 2) | Poor risk disease (IMDC score of 3-6) |
|---|---|---|
| 6 months | 88% (95% CI: 84% to 90%) | 67% (95% CI: 61% to 72%) |
| 12 months | 76% (95% CI: 72% to 80%) | 55% (95% CI: 49% to 61%) |
| 18 months | 69% (95% CI: 64% to 73%) | 45% (95% CI: 38% to 51%) |

CI=confidence interval; IMDC=International Metastatic Database Consortium; OS=overall survival; SACT=Systemic Anti-Cancer Therapy
Source: SACT report,[6] Table 23

Table 12 SACT dataset treatment duration data

| Time period | Intermediate risk disease (IMDC score of 1 or 2) | Poor risk disease (IMDC score of 3-6) |
|---|---|---|
| 6 months | 52% (95% CI: 48% to 57%) | 41% (95% CI: 35% to 47%) |
| 12 months | 41% (95% CI: 36% to 46%) | 26% (95% CI: 20% to 32%) |
| 18 months | 29% (95% CI: 23% to 35%) | 19% (95% CI: 13% to 26%) |

CI=confidence interval; IMDC=International Metastatic Database Consortium; SACT=Systemic Anti-Cancer Therapy
Source: SACT report,[6] Table 19

### *4.4 ERG revisions to the company model*

The ERG has generated two scenarios to explore the impact of equalising company model mortality hazards for patients in the NIVO+IPI and sunitinib (or pazopanib) arms from Month 54 onwards. In the first scenario, the mortality hazards for the NIVO+IPI arm have been set equal to the mortality hazards for the sunitinib (or pazopanib) arm. In the second scenario, the mortality hazards for the sunitinib (or pazopanib) arm have been set equal to the mortality hazards for the NIVO+IPI arm. As, in the company base case, the mortality hazards for the NIVO+IPI arm are always lower than the mortality hazards for the sunitinib (or pazopanib) arm, the first scenario reduces OS for the NIVO+IPI arm, leaving the OS for sunitinib (or pazopanib) unchanged and the second scenario increases the OS for the sunitinib (or pazopanib) arm, leaving OS for the NIVO+IPI arm unchanged. The available CheckMate 214 trial and SACT data do not suggest that one scenario is more plausible than the other.

Results for the comparison of NIVO+IPI versus sunitinib are presented in Table 13. Results for the comparison of NIVO+IPI versus pazopanib (the analysis assumes that the only difference between sunitinib and pazopanib is the cost of the two drugs) are presented in Table 14.

The instructions for implementing the ERG's revisions in the company model are presented in the Appendix.

Table 13 ERG scenarios for comparison of NIVO+IPI versus sunitinib (PAS price for nivolumab, ipilimumab and sunitinib)

| Scenarios | NIVO+IPI | | | Sunitinib | | | Incremental | | | ICER (£/QALY gained) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | Life years | QALYs | Cost | Life years | QALYs | Cost | Life years | QALYs | |
| **A. Company base case** | [redacted] | **8.083** | **4.620** | [redacted] | **5.349** | **3.131** | **£38,541** | **2.734** | **1.489** | **£25,827** |
| S1 Mortality hazard for NIVO+IPI set equal to mortality hazards for sunitinib from month 54 onwards | [redacted] | 6.896 | 4.132 | [redacted] | 5.349 | 3.131 | £36,082 | 1.547 | 1.001 | £36,041 |
| S2 Mortality hazards for sunitinib set equal to mortality hazards for NIVI+IPI from month 54 onwards | [redacted] | 8.083 | 4.620 | [redacted] | 6.199 | 3.474 | £36,735 | 1.885 | 1.145 | £32,073 |

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CDF Review CS and ERG adjusted company model

Table 14 ERG scenarios for comparison of NIVO+IPI versus pazopanib (PAS price for nivolumab, ipilimumab and pazopanib)

| Scenarios | NIVO+IPI | | | Pazopanib | | | Incremental | | | ICER (£/QALY gained) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | Life years | QALYs | Cost | Life years | QALYs | Cost | Life years | QALYs | |
| **A. Company base case** | [redacted] | **8.083** | **4.620** | [redacted] | **5.349** | **3.131** | **£36,539** | **2.734** | **1.489** | **£24,543** |
| S1 Mortality hazards for NIVO+IPI set equal to mortality hazards for pazopanib from month 54 onwards | [redacted] | 6.896 | 4.132 | [redacted] | 5.349 | 3.131 | £34,170 | 1.574 | 1.001 | £34,132 |
| S2 Mortality hazards for pazopanib set equal to NIVI+IPI from month 54 onwards | [redacted] | 8.083 | 4.620 | [redacted] | 6.199 | 3.474 | £34,824 | 1.885 | 1.145 | £30,404 |

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CDF Review CS and ERG adjusted company model

### *4.5 Cost effectiveness conclusions*

The company has been able to provide evidence to address most of the points raised by the NICE Appraisal Committee (as set out in the ToE[3]). However, the ERG considers that the company model OS projections for patients who received NIVO+IPI in the first-line setting are not plausible; the ERG has adjusted the company base case OS model projections so that they are more in line with CheckMate 214 trial data.

There are differences between the proportions of poor-risk patients in the CheckMate 214 trial and in the SACT dataset. If the NICE Appraisal Committee considers that this difference means that the CheckMate 214 trial results are not generalisable to the NHS, then the cost effectiveness results presented by the company and the ERG are unlikely to be generalisable to the NHS.

# 5 REFERENCES


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# 6 APPENDIX: ERG model amendments

**Scenario 1**

In sheet "OS". In cell BN265 enter formula “=BN264*BO265/BO264”. Copy cell formula to range BN266:BN2152

**Scenario 2**

In sheet "OS". In cell BO265 enter formula “=BO264*BN265/BN264”. Copy cell formula to range BO266:BO2152

**National Institute for Health and Care Excellence**

**Centre for Health Technology Evaluation**

## ERG report – factual accuracy check and confidential information check

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 21 October** using the below 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

## Issue 1 SACT factual inaccuracies

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Stated in section 2.3, page 11 "The company considers that data from the latest data-cuts of these two sources provide sufficient evidence to address the NICE Appraisal Committee's main uncertainties"<br><br>BMS do not believe the SACT data provide sufficient evidence to address the uncertainties raised and should not be considered for decision making. | "The company considers that data from the latest cut of CheckMate 214 provides sufficient evidence to address the NICE appraisal Committee's main uncertainties." | Factual inaccuracy | Text amended in line with company suggestion |
| Stated in section 2.3.2, page 13 "Data are available for the 814 patients with a SACT database treatment record for a maximum period of 24 months". The CDF SACT period was 24 months, and the SACT report only considered applications for NIVO+IPI between 4 April 2019 and 30 November 2020. | The ERG should acknowledge that the "CDF SACT period was 24 months and considered applications for NIVO+IPI between 4 April 2019 and 30 November 2020. Patients were traced for their vital status on 28 April 2021" | Factual inaccuracy | The additional information highlighted by the company has been added to the ERG report |
| Page 15 Table 4, the age range reported for the SACT dataset is incorrect. It states the age range for SACT as being patients aged 60 to 63 years. This is the median age in males and females (60 and | Remove the median age range from page 15 Table 4 for SACT patients as this is not reported in the SACT report. Instead the ERG should include point from SACT report page 39 that states '85% of the cohort were aged | Factual inaccuracy | Table amended to show median for males, median for females and overall median |

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| 63 years respectively) not the age range of patients. | between 50 and 79 years of age (N=695)' if detail on age distribution is required. | | |
| Stated in page 18, Table 8 "First subsequent treatments for SACT dataset patients treated with NIVO+IPI (24 months)". The CDF period is 24 months, but consistent terminology should be used when discussing data cuts to avoid misinterpretation, particularly as the CheckMate 214 data has a minimum follow-up of 60 months. | Table heading should read "First subsequent treatments for SACT dataset patients treated with NIVO+IPI (minimum follow-up 5 months)" | Factual inaccuracy | Heading text of Table 8 amended. Also, 'minimum follow up' added to the headings of Table 7 |
| Stated in section 3.4, page 19 "A comparison of 30-month CheckMate 214 trial data and 24-month SACT[6] data". As mentioned above the CDF period is 24 months, but consistent terminology should be used when discussing data cuts to avoid misinterpretations, particularly as the CheckMate 214 data has a minimum follow-up of 60 months. | "A comparison of 30-month minimum follow-up CheckMate 214 trial data and 5-month minimum follow-up SACT[6] data" | Factual inaccuracy | Text amended in line with company suggestion<br>Words 'minimum follow up' added where comparisons between data sets have been made:<br>• Table 1 headings<br>• Page 19 ("The ERG considers that a comparison of 30-month minimum follow-up CheckMate 214 trial data and 5-month minimum follow-up SACT[6] data (**Error! Reference source not found.** and **Error! Reference source not found.**) shows…"<br>• Section 4.1.1 ("…using the 60-month minimum follow- |

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| | | | up CheckMate 214 trial K-M data." and "…(using 30-month minimum follow-up CheckMate 214 trial data)" |
| Stated in section 3.4, page 19 "CheckMate 214 trial do not match the subsequent treatments received by the patients who received NIVO+IPI in the NHS"<br>and<br>"CheckMate 214 trial patients may be more heavily treated than SACT[6] patients"<br>It is inappropriate to compare 30 months minimum data with 5 months minimum data. | We propose that these sentences should be removed. | Factual inaccuracy | Text amended to emphasise that this is the ERG's opinion<br>The bullet point:<br>"CheckMate 214 trial patients may be more heavily treated than SACT[6] patients"<br>has been deleted |
| Stated in section 3.4, page 19 "none of the CheckMate 214 trial patients received a combination therapy."<br>CheckMate 215 subsequent treatments show that more than one therapy may have been received. | We propose that this sentence should be removed. | Factual inaccuracy | This is not a factual inaccuracy. No change required |
| Stated on section 3.4, page 19 "SACT data only relate to first subsequent treatment". The SACT report does provide data on other subsequent therapies (SACT Report Table 7) and includes the | The ERG should acknowledge the SACT report does provide data on other line of subsequent therapies. | Factual inaccuracy | This is not a factual inaccuracy; however, the ERG has added a footnote to Table 8 to add clarity |

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| distribution of further lines of therapy. | | | |

## Issue 2 Overall survival estimates

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 7, section 1.2, issue 1, the ERG refer to data as "60-month follow-up OS data". | This should be represented as" 60-month minimum follow-up OS data" to avoid misinterpretation | Factual inaccuracy | Text amended as suggested |
| Section 2.3.1, page 12 "The survival data used to inform the CDF Review CS are 60-month follow-up CheckMate 214" | "The survival data used to inform the CDF Review CS are 60-month minimum follow-up CheckMate 214" | Factual inaccuracy | Text amended as suggested |
| Section 4.1, page 23 states: "In the company base case, compared with patients treated with sunitinib, 82% of the OS gain (and 66% of the quality adjusted life year [QALY] gain) for patients treated with NIVO+IPI occurs during the period between 61 months and the end of the model time horizon (480 months)"<br><br>The company are unable to match these results and recommend that the ERG provide detail on their calculations | The company are unable to match these results and recommend that the ERG provide detail on their calculations. It would be beneficial to clarify that the majority of incremental clinical benefit associated with NIVO+IPI is still being accrued in the PFS state, with a larger number of LYs and QALYs being accrued by the comparator in the PPS state, in the company base case. | ERG to update wording in order to avoid any misinterpretation of the evidence. | In the company model, the total OS and QALY gains for patients in the NIVO+IPI arm over the 40-year time horizon are [redacted] years and [redacted] QALYs respectively. Setting the model time horizon to 5 years results in an OS gain for patients in the NIVO+IPI arm of [redacted] years and a QALY gain of [redacted] QALYs. So, at 5 years (60 months), patients in the NIVO+IPI arm have experienced [redacted]% of lifetime OS gain ([redacted] years) and [redacted]% of lifetime QALY gain ([redacted] QALYs). The text has been amended as follows: |

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| | | | "In the company base case, compared with patients treated with sunitinib, [redacted] % of the OS gain (and [redacted] % of the quality adjusted life year [QALY] gain) for patients treated with NIVO+IPI occurs during the period between 61 months and the end of the model time horizon (480 months)…" |
| Statements in section 4.1.2, page 25 would benefit from additional clarity to avoid misinterpretation. The ERG states "It, therefore, seems entirely (clinically) plausible to expect that, over time, patients who are still alive will have received NIVO+IPI and/or sunitinib and will have similar mortality hazards regardless of their first-line treatment ." | Suggest changing the sentence to "It, therefore, seems entirely (clinically) plausible to expect that, over time, patients who are still alive <u>after progression and require subsequent treatment</u> will have received NIVO+IPI and/or sunitinib and will have similar mortality hazards regardless of their first-line treatment" | To clarify that the statement relates to the post-progression period and the need for subsequent treatment. | For clarity, the sentence has been replaced with the following text:<br><br>"Therefore, if NIVO+IPI is more effective in terms of extending OS than sunitinib, the subsequent treatments received by patients enrolled in the CheckMate 214 trial would not support modelling lower mortality rates in the NIVO+IPI arm of the model than in the sunitinib arm of the model beyond Year 4. Conversely, superior effectiveness, in terms of OS, of NIVO+IPI versus sunitinib would support modelling equal hazards in both arms, or for mortality rates in the NIVO+IPI arm being higher |

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| | | | than in the sunitinib arm beyond Year 4." |
| Page 24 figure 24: Only part of Figure 3 has been provided and the title is incorrect from that provided in CS | The entire Figure 3 should be included, including plots for NIVO+IPI and sunitinib, and the full figure should be marked as AIC.<br>The title should be corrected to "CheckMate 214 overall survival smoothed for NIVO+IPI and sunitinib using the 48-month and 60-month data cuts, along with unsmoothed hazard plots for NIVO+IPI (left) and sunitinib (right)" | Factual inaccuracy | The wrong figure was included in the ERG report. Figure 2 from the company clarification response should have been used (unsmoothed hazard rates). The correct figure has been inserted into the ERG report |
| Section 4.1.2, page 25 states "However, Year 6 data do not support a conclusion that the NIVO+IPI arm mortality rate is lower than the sunitinib arm rate..". These statements are misleading. | We propose that the second sentence should be removed and the year 6 row be removed from Table 10. | Year 6 CheckMate214 trial data cannot be reliably used or interpreted alone due to the heavy censoring at year 6, with just 2 patients at risk in the N+I arm and 3 patients at risk in the SUN arm, and the statement as written by the ERG currently is misleading. | This is not a factual inaccuracy. No change required |
| Section 4.1.2,, page 26 states "there is no censoring before Month 60 and so the hazard ratio (HR) between Month 48 and Month 60 is completely unaffected by censoring". This statement is factually inaccurate. | The quoted sentence on Page 26 should be removed, and suggest a sentence to reflect the effect of censoring on the hazards after 48 months "The period between month 48 and month 60 on the smoothed hazard plot is affected by censoring. The smoothing interval used for the hazard plots is 12 months, therefore the impact of heavy censoring after 60 months is observed after 48 months in the smoothed hazard plot." | It is a factual inaccuracy to state there is no censoring before 60 months minimum follow-up in CheckMate 214. The smoothing interval used for the smoothed hazard plots is 12 months, therefore the impact of heavy censoring after 60 months is observed after 48 months in the smoothed hazard plot. The period between month 48 and month 60 | The hazards calculated by the ERG relate to unsmoothed hazard rates and so the text has been changed to:<br><br>"However, as a minimum of 60 months follow-up data are available from the CheckMate 214 trial, there is no censoring before Month 60 and so the unsmoothed hazard rates between Month 48 and Month |

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| | | on the smoothed hazard plot is affected by censoring. | 60 are completely unaffected by censoring.” |

## Issue 3 Evidence Sources

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Section 2.3, page 11 states: “The two main sources of evidence for this review are the CheckMate 214 trial and Systemic Anti-Cancer Therapy (SACT) data.” | The main source of evidence in the submission is CheckMate 214: suggest changing to “the main source of evidence for this review is the CheckMate 214 trial” | As stated in the FAD for TA581, section 3.24, page 20 “It [the committee] also concluded that the SACT database would supplement the additional evidence from CheckMate 214 and validate some modelled parameters.” This is also reflected in the Managed Access agreement for TA581 page **1** “**Primary source of data collection:** Ongoing clinical study (CheckMate 214)<br><br>**Secondary source of data collection:** Systemic Anti-Cancer Therapy data set (SACT)”<br><br>The main source of data in the re-submission is the CheckMate 214 trial, therefore, it is an inaccuracy to state that there are two main sources of evidence for this review. | For clarity, text amended |

## Issue 4 Clarification Points

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Section 3.2, page 17 states: "and the comparators for the intermediate- and poor-risk populations only are cabozantinib and NIVO+IPI" | We would like to seek clarification as to whether sunitinib, pazopanib and tivozanib are considered comparators in the intermediate/poor-risk group. | BMS would like clarification as to this point. | Text amended to clarify that sunitinib, pazopanib and tivozanib are considered comparators in the intermediate- and poor-risk group |
| Section 3.4, page 19 states: "Further, if NIVO+IPI were to be recommended by NICE, there is only one NICE recommended second-line treatment for this group of patients (i.e., nivolumab is a treatment option for previously treated advanced RCC [TA417]"<br><br>Similarly, "The subsequent treatments for NHS patients who would receive NIVO+IPI in the first-line setting (if recommended by NICE) are unclear." on section 3.4, page 19 | We propose that this should be removed. | The NHS England letter during the initial appraisal of TA581 highlighted their expectation to the change in subsequent therapies should NIVO+IPI be recommended. Such changes included sunitinib and pazopanib being moved to a later line of therapy | This is not a factual inaccuracy. No change required |
| Section 4.3, page 27 states:"… and the consequent focus on treating sicker patients" and "suggesting that there was no focus on only treating the sickest patients" | BMS do not suggest that there is a focus on treating sicker patients but suggest that patients would be sicker in general due to treatment delays and diagnoses potentially coming later. | Misinterpretation- the submissions suggests that patients would be sicker in general due to treatment delays and diagnoses potentially coming later. | Text amended in line with company suggestion |
| Section 4.3, page 27 it states: "The ERG considers that the SACT dataset is a fair reflection | We propose that this sentence should be removed. | There is no significant justification in light of the available evidence or | Text changed to: "The ERG considers that the SACT |

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| of the ratio between intermediate- and poor-risk patients who would be treated with NIVO+IPI in the NHS." | | rationale for this comment and it risks misrepresenting the generalisability of the SACT data. | dataset may be a fair reflection…" |

## Issue 5 Typographical grammatical errors

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 2: "Copyright is retained by Bristol-Myers Squib for Table A and Table B" | "Copyright is retained by Bristol Myers Squibb for Table A and Table B" | Typographical error | Amended - apologies |
| Page 7, section 1.2, issue 1 "The effect of the ERG changes is to increase the company base case cost effectiveness results" | "The effect of the ERG changes is to increase the company base case cost-effectiveness results" | Typographical error | This is not an error |
| Section 2.1, page 11 "International Metastatic Renal Cell Carcinoma Database Consortium (IDMC)" | "International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)" | Typographical error | Amended |
| Section 2.3.1 Table 1 page 13 "Initial CS (30 months)" for Progression-free survival (IRRC secondary definition) should be 18 months as PFS secondary definition available at 18 months. | For Progression-free survival (IRRC secondary definition) should be "Initial CS (18 months)" | Typographical error | Amended |
| Section 3.1, page 14 "All results presented in this ERG report relate only to the intermediate- and poor-risk groups." | "All results presented in this ERG report relate only to the intermediate- and poor-risk group." | Typographical error | Amended |
| Section 3.1, page 14 "NHS clinical practice than the patients | NHS clinical practice than the patients enrolled in the CheckMate 214 trial. | Typographical error | Amended |

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| enrolled in the Checkmate 214 trial." | | | |
| Page 15, Table 4<br>"Patient baseline characteristics: CheckMate 2014 trial and SACT database" | "Patient baseline characteristics: CheckMate 214 trial and SACT database" | Typographical error | Amended |
| Section 3.5, page 19<br>"cabzantinib" | "cabozantinib" | Typographical error | Amended |
| Page 29, Table 14 "pazotinib" | "pazopanib" | Typographical error | Amended |

Public Health England

Protecting and improving the nation's health

# Nivolumab with ipilimumab for treating untreated intermediate or poor risk advance renal cell carcinoma – data review

Commissioned by NHS England and NHS Improvement

# Contents

# Executive summary

## Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of nivolumab with ipilimumab for untreated intermediate or poor risk advanced renal cell carcinoma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended the commissioning of nivolumab with ipilimumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of nivolumab with ipilimumab for the 1st line treatment of intermediate or poor risk advanced renal cell carcinoma in the CDF, during the managed access period. This report presents the results of the use of nivolumab with ipilimumab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 64% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

## Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for nivolumab with ipilimumab for untreated intermediate or poor risk advanced renal cell carcinoma in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 4 April 2019 and 30 November 2020, 897 applications for nivolumab with ipilimumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 821 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

# Results

814 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration for all patients was 5.5 months [95% CI: 4.3, 7.0] (167 days). 48% of patients were still receiving treatment at 6 months [95% CI: 45%,52%], 35% of patients were still receiving treatment at 12 months [95% CI: 31%, 39%] and 25% of patients were still receiving treatment at 18 months [95% CI: 21%, 30%].

At data cut off, 58% (N=469) of patients were identified as no longer being on treatment. Of these 469 patients, 27% (N=128) of patients stopped treatment due to progression, 20% (N=94) of patients stopped treatment due to acute toxicity, <1% (N=2) of patients chose to end their treatment, 28% (N=131) of patients died not on treatment, 5% (N=24) of patients died on treatment, 5% (N=23) of patients completed treatment as prescribed, <1% (N=2) of patients stopped treatment due to COVID and 14% (N=65) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median OS was not reached. OS at 6 months was 80% [95% CI: 77%, 83%], OS at 12 months was 69% [95% CI: 65%, 72%] and OS at 18 months was 61% [95% CI: 57%, 64%].

A sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results for treatment duration showed a difference of 1.2 months. The median OS was not reached in either cohort. A secondary sensitivity analysis was also conducted to show treatment duration and OS by International Metastatic RCC Database Consortium (IMDC) score where the results were statistically significantly different.

# Conclusion

This report analysed SACT real-world data for patients treated with nivolumab with ipilimumab for untreated intermediate or poor risk advanced renal cell carcinoma in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with nivolumab with ipilimumab for this indication.

# Introduction

Renal cell carcinoma (ICD-10 C64) accounts for 3% of all cancer diagnoses in England. In 2018, 9,438 patients were diagnosed with renal cell carcinoma (males 6,059, females 3,379)[2].

- Nivolumab with ipilimumab is recommended for use within the Cancer Drugs Fund as an option for adults with untreated advanced renal cell carcinoma that is intermediate or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria. It is recommended only if the conditions in the managed access agreement for nivolumab with ipilimumab are followed[3].

# Background to this report

## The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

## NICE Appraisal Committee review of nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma [TA581].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of nivolumab with ipilimumab (BMS) in treating untreated intermediate or poor risk advanced renal cell carcinoma [TA581] and published guidance for this indication in May 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of nivolumab with ipilimumab for the 1st line treatment of intermediate or poor risk advanced renal cell carcinoma through the CDF for a period of 24 months, from April 2019 to April 2021.

During the CDF funding period, results from an ongoing clinical trial (CheckMate 214[7]) evaluating nivolumab with ipilimumab in the licensed indication are likely to answer the main

clinical uncertainties raised by the NICE committee. Data collected from the CheckMate 214 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for nivolumab with ipilimumab for untreated intermediate or poor risk advanced renal cell carcinoma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the CheckMate 214[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Treatment duration** for the use of nivolumab with ipilimumab
- **Overall survival** from the start of a patient's first treatment with nivolumab with ipilimumab
- **Subsequent therapies used in clinical practice**

## Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (BMS) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma. It also detailed the eligibility criteria for patient access to nivolumab with ipilimumab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for nivolumab with ipilimumab, approved through Blueteq® and followed up in the SACT dataset collected by PHE.

# Methods

## CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

## Nivolumab with ipilimumab clinical treatment criteria

- Patient has unresectable locally advanced or metastatic renal cell adenocarcinoma (RCC) which either has a clear cell component or is a papillary RCC.
- No prior systemic therapy for locally advanced/metastatic RCC with the following exception of in the context of clinical trials investigating adjuvant therapies for completely resectable RCC.
- Patient has a prognosis considered either intermediate or poor-risk as per the International Metastatic RCC Database Consortium (IMDC) system, which scores 1 point for each of the following 6 factors. A score of 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk. The IMDC factors are:
    - Karnofsky performance status of less than 80%
    - Less than 1 year from time of initial diagnosis to now
    - Haemoglobin less than the lower limit of normal (LLN)
    - Corrected calcium concentration greater than >2.5mmol/L
    - Absolute neutrophil count greater than the upper limit of normal (ULN)
    - Platelet count greater than the ULN
- Patient has a Karnofsky performance status of at least 70%.
- No symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
- Patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner.
- Ipilimumab will be used at the RCC ipilimumab dose of 1mg/Kg every 3 weeks for a maximum of four 3-weekly cycles.
- Nivolumab will be used at a dose of 3mg/Kg every 3 weeks for the first 4 cycles (i.e. when in combination with ipilimumab) and then as subsequent monotherapy at a fixed dose of either 240mg every 2 weeks or 480mg every 4 weeks.
- A formal medical review to assess the tolerability of treatment with nivolumab and ipilimumab will be scheduled to occur by the start of the 3rd 3-weekly cycle of treatment and thereafter on a regular basis.
- Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any toxicities to settle.
- Nivolumab and ipilimumab are otherwise to be used as set out in their Summary of Product Characteristics.

## CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for nivolumab with ipilimumab for the treatment of untreated intermediate or poor risk advanced renal cell carcinoma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for nivolumab with ipilimumab for the treatment of untreated intermediate or poor risk advanced renal cell carcinoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for nivolumab with ipilimumab for the treatment of untreated intermediate or poor risk advanced renal cell carcinoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

## Initial CDF cohorts

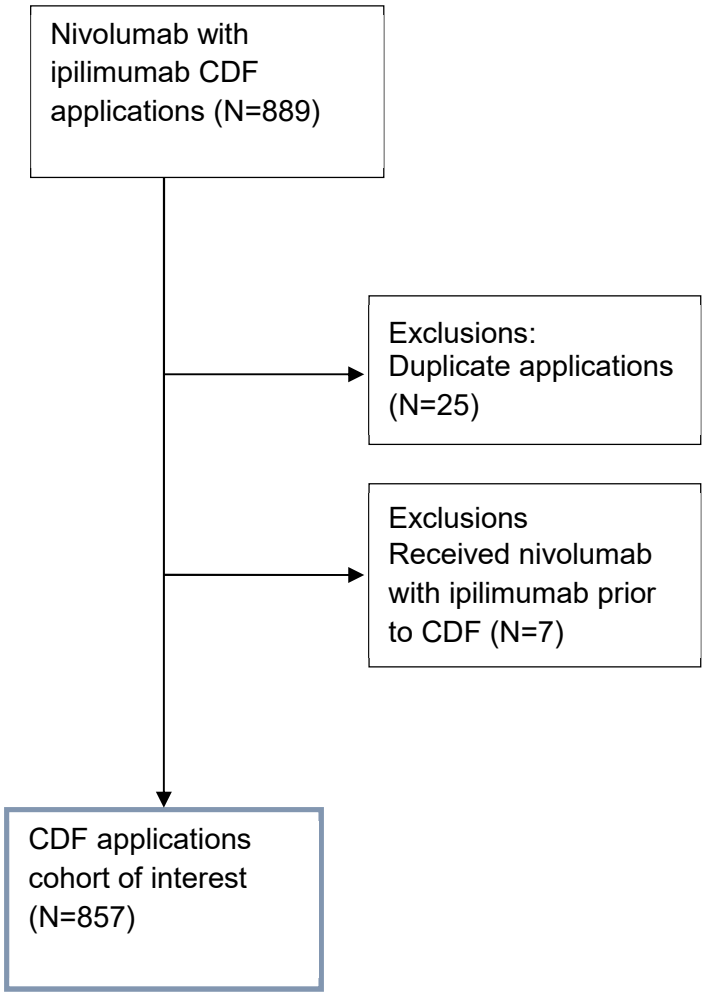
The analysis cohort is limited to the date nivolumab with ipilimumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 4 April 2019 and 30 November 2020. A snapshot of SACT data was taken on 6 March 2021 and made available for analysis on 12 March 2021 and includes SACT activity up to the 30 November 2020. Tracing the patients' vital status was carried out on 28 April 2021 using the Personal Demographics Service (PDS)[1].

There were 889 applications for CDF funding for nivolumab with ipilimumab for the treatment of untreated intermediate or poor risk advanced renal cell carcinoma between 4 April 2019 and 30 November 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 864 unique patients.

Seven patients were excluded from these analyses as they appeared to have received nivolumab with ipilimumab prior to the drug being available through the CDF.

**Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma between 4 April 2019 and 30 November 2020.**




## Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for nivolumab with ipilimumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

# Addressing clinical uncertainties

## Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

**Start date of regimen**
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

**Start date of cycle**
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

**Administration date**
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between

administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Nivolumab with ipilimumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that treatment administration has taken place on a specified date. A duration of 27, 20 or 13 days has been added to the final treatment date for all patients, depending on the prescribing schedule they are on; this represents the duration from a patient's last cycle to their next[9].

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

## Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

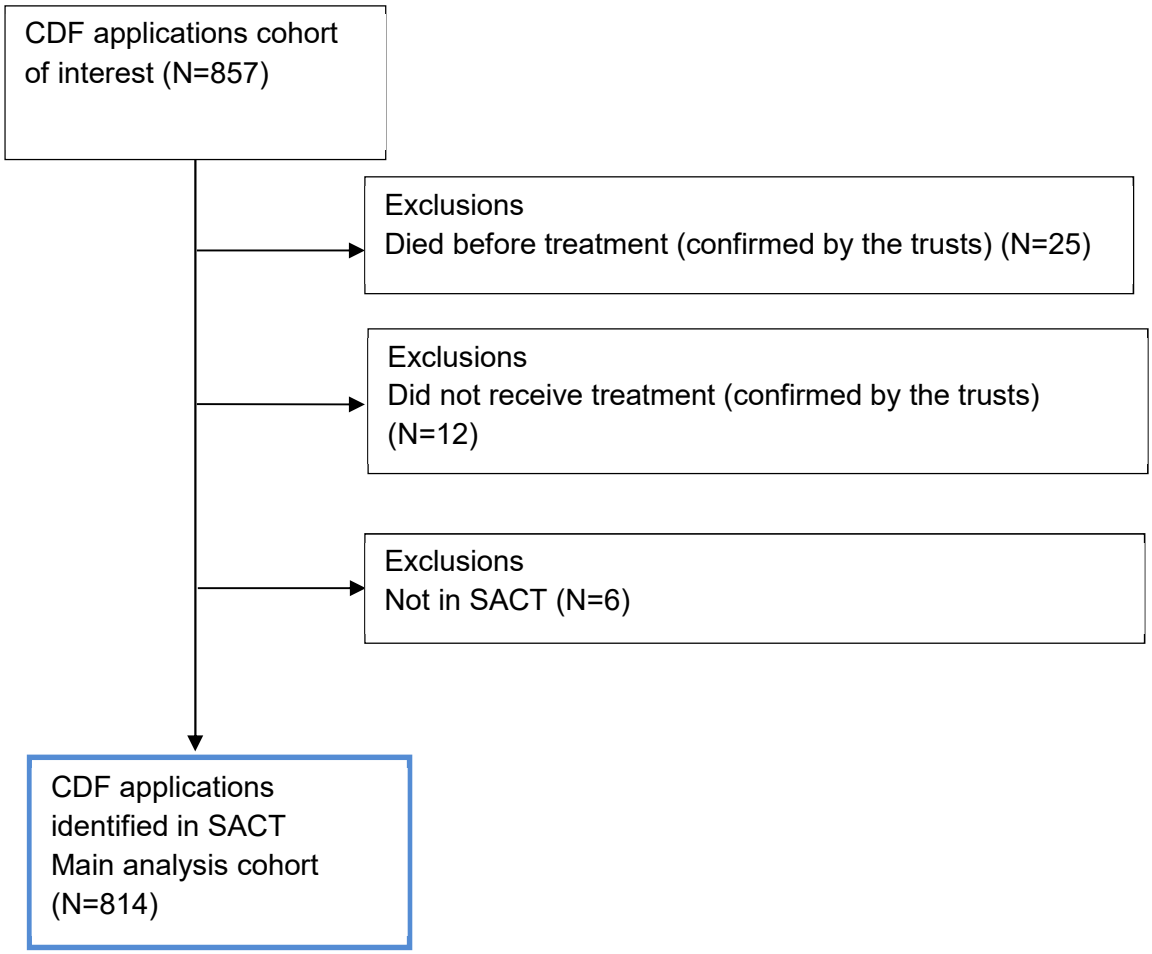
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

# Results

## Cohort of interest

Of the 857 new applications for CDF funding for nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma, 12 patients did not receive treatment, 25 patients died before treatment and six patients were missing from SACT[a] (see Figure 2).

**Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma between 5 April 2019 and 30 November 2020**




A maximum of 820 nivolumab with ipilimumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99% (814/820) of these applicants for CDF funding have a treatment record in SACT.

[a] Of the 12 patients that did not receive treatment, all were confirmed by the relevant trust by the PHE data liaison team. Of the 25 patients that died before treatment, all were confirmed by the relevant trusts by the PHE data liaison team.

## Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 92% complete.

**Table 1. Completeness of key SACT data items for the nivolumab with ipilimumab cohort (N=814)**

| Variable | Completeness (%) |
|---|---|
| Primary diagnosis | 100% |
| Date of birth (used to calculate age) | 100% |
| Sex | 100% |
| Start date of regimen | 100% |
| Start date of cycle | 100% |
| Administration date | 100% |
| Performance status at start of regimen | 92% |

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with nivolumab with ipilimumab in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 469 patients. Of these, 302 (64%) have an outcome summary recorded in the SACT dataset.

**Table 2. Completeness of outcome summary for patients that have ended treatment (N=469)**

| Variable | Completeness (%) |
|---|---|
| Outcome summary of why treatment was stopped | 64% |

## Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. All Blueteq data items were 100% complete.

**Table 3: Completeness of key Blueteq data items for the nivolumab with ipilimumab cohort (N=814)**

| Variable | Completeness (%) |
|---|---|
| Histology type | 100% |
| Previous treatments received in an adjuvant setting | 100% |
| IMDC prognostic factors | 100% |

## Patient characteristics

The median age of the 814 patients receiving nivolumab with ipilimumab for treating untreated intermediate or poor risk advanced renal cell carcinoma was 61 years. The median age in males and females was 60 and 63 years respectively.

**Table 4. Patient characteristics (N=814)**

| Patient characteristics[b] | | | |
|---|---|---|---|
| | | **N** | **%** |
| Sex | Male | 596 | 73% |
| | Female | 218 | 27% |
| Age | <40 | 15 | 2% |
| | 40 to 49 | 96 | 12% |
| | 50 to 59 | 257 | 32% |
| | 60 to 69 | 271 | 33% |
| | 70 to 79 | 167 | 21% |
| | 80+ | 8 | 1% |
| Performance status | 0 | 285 | 35% |
| | 1 | 420 | 52% |
| | 2 | 41 | 5% |
| | 3 | 1 | <1% |
| | 4 | 0 | 0% |
| | Missing | 67 | 8% |

[b] Figures may not sum to 100% due to rounding.

# Blueteq data items

Table 5 shows the distribution of Blueteq data items: Histology type, previous treatments and IMDC prognostic factors.

**Table 5: Distribution of key Blueteq data items (N=814)**

| Blueteq data items[c] | | | |
|---|---|---|---|
| | | **N** | **%** |
| Histology type | RCC with a clear cell component | 740 | 91% |
| | Papillary RCC | 74 | 9% |
| Previous treatments | No previous adjuvant systemic therapy of any kind | 804 | 99% |
| | Prior clinical trial with adjuvant therapy with immune-modulatory therapies | 5 | 1% |
| | prior clinical trial with adjuvant therapy with agents which target VEGF | 5 | 1% |
| IMDC prognostic factors | Intermediate risk disease (IMDC score of 1 or 2) | 533 | 65% |
| | Poor risk disease (IMDC score of 3-6) | 281 | 35% |

[c] Figures may not add to 100% due to rounding.

## Time to subsequent treatments in SACT

234/814 (29%) unique patients treated with nivolumab with ipilimumab in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last nivolumab with ipilimumab cycle. Table 6 reports regimens prescribed after nivolumab with ipilimumab, as recorded in the SACT dataset, some patients have more than one subsequent therapy, these regimens are shown in Table 7.

The median time from a patient's last nivolumab with ipilimumab cycle in SACT to their next treatment was 41 days[d].

The median time from a patient's first nivolumab with ipilimumab cycle in SACT to their next treatment was 148 days.

## Distribution of subsequent treatments in SACT

**Table 6: Distribution of first treatments prescribed after a patient's last nivolumab with ipilimumab cycle (N(Patients)=234)** [e,f]

| Regimen | Number of subsequent treatments |
|---|---|
| Cabozantinib | 139 |
| Sunitinib | 31 |
| Pazopanib | 28 |
| Tivozanib | 19 |
| Axitinib | 6 |
| Everolimus + lenvatinib | 5 |
| Dabrafenib + trametinib | 2 |
| Carboplatin + pemetrexed | 1 |
| Everolimus | 1 |
| Irinotecan + mdg + panitumumab | 1 |
| Trial | 1 |
| **Total number of subsequent treatments** | **234** |

[d] If a patient has > 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen immediately after nivolumab with ipilimumab.
[e] Some patients will have received more than one subsequent therapy. Table 6 lists therapies prescribed immediately after a patient's last nivolumab with ipilimumab cycle. Subsequent therapies could be related to a second primary tumour.
[f] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

**Table 7: Distribution of further lines of therapy following a patient's last nivolumab with ipilimumab cycle (N(Patients)=234) [g,h]**

| Regimen | Number of subsequent treatments |
|---|---|
| Everolimus + lenvatinib | 13 |
| Cabozantinib | 6 |
| Sunitinib | 5 |
| Axitinib | 3 |
| Everolimus | 2 |
| Lenvatinib | 1 |
| Oxaliplatin + mdg + panitumumab | 1 |
| Pazopanib | 1 |
| Tivozanib | 1 |
| **Total number of subsequent treatments** | **33** |

[g] Some patients will have received more than one subsequent therapy. Table 7 lists further lines of therapies prescribed after a patient's last nivolumab with ipilimumab cycle in SACT. Subsequent therapies could be related to a second primary tumour.
[h] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

## Treatment duration

Of the 814 patients with CDF applications, 469 (58%) were identified as having completed treatment by 30 November 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with nivolumab with ipilimumab in at least three months (see Table 11). The median follow-up time in SACT was 3 months (91 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 19.9 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 20.9 months. SACT follow-up ends 30 November 2020.

**Table 8: Breakdown by patients' treatment status[i,j,k]**

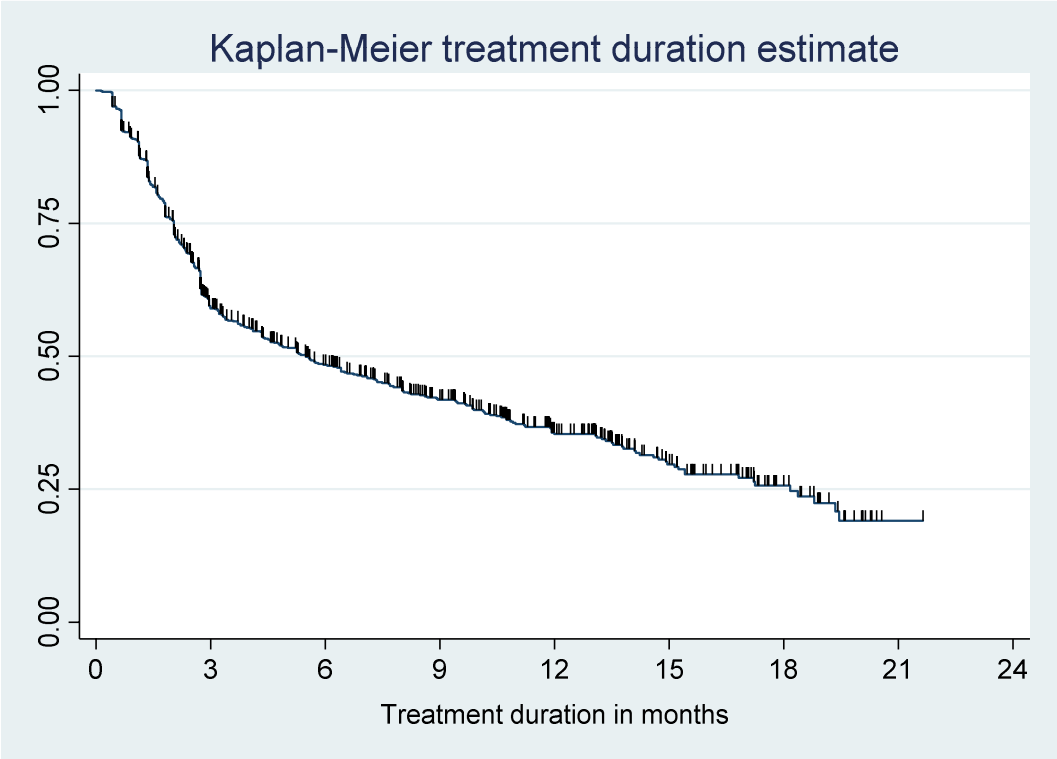
| Patient status | Frequency (N) | Percentage (%) |
|---|---|---|
| Patient died – not on treatment | 254 | 31% |
| Patient died – on treatment | 24 | 3% |
| Treatment stopped | 191 | 23% |
| Treatment ongoing | 345 | 42% |
| **Total** | **814** | **100%** |

[i] Figures may not sum to 100% due to rounding.
[j] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[k] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 5.5 months [95% CI: 4.3, 7.0] (167 days) (N=814).

48% of patients were still receiving treatment at 6 months [95% CI: 45%,52%], 35% of patients were still receiving treatment at 12 months [95% CI: 31%, 39%] and 25% of patients were still receiving treatment at 18 months [95% CI: 21%, 30%].

**Figure 3. Kaplan-Meier treatment duration (N=814)[l]**




Tables 9 and 10 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19.9 months (605 days). SACT contains more follow-up for some patients.

[l] The last SACT date used was assigned to a nivolumab with ipilimumab or nivolumab monotherapy regimen, whichever occurred later.

**Table 9. Number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| Number at risk | 814 | 395 | 283 | 202 | 126 | 65 | 26 | 1 |

Table 10 shows that for all patients who received treatment, 345 were still on treatment (censored) at the date of follow-up and 469 had ended treatment (events).

**Table 10. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| Censored | 345 | 239 | 194 | 148 | 99 | 53 | 21 | 1 |
| Events | 469 | 156 | 89 | 54 | 27 | 12 | 5 | 0 |

Table 11 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 58% (N=469) of patients had ended treatment at 30 November 2020.

**Table 11: Treatment outcomes for patients that have ended treatment (N=469)[m],[n]**

| Outcome | Frequency (N) | Percentage (%) |
|---|---|---|
| Stopped treatment – died not on treatment[o] | 131 | 28% |
| Stopped treatment – progression of disease | 128 | 27% |
| Stopped treatment – acute toxicity | 94 | 20% |
| Stopped treatment – no treatment in at least 3 months | 65 | 14% |
| Stopped treatment – died on treatment | 24 | 5% |
| Stopped treatment – completed as prescribed | 23 | 5% |
| Stopped treatment – patient choice | 2 | <1% |
| Stopped treatment – COVID | 2 | <1% |
| **Total** | **469** | **100%** |

[m] Figures may not sum to 100% due to rounding.
[n] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[o] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

**Table 12: Treatment outcomes and treatment status for patients that have ended treatment (N=469)**

| Outcome[p] | Patient died [q] not on treatment | Treatment stopped | Patient died on treatment |
|---|---|---|---|
| Stopped treatment – progression of disease | 77 | 51 | |
| Stopped treatment – acute toxicity | 39 | 55 | |
| Stopped treatment – patient choice | 2 | | |
| Stopped treatment – died not on treatment | 131 | | |
| Stopped treatment – died on treatment | | | 24 |
| Stopped treatment – completed as prescribed | 5 | 18 | |
| Stopped treatment - COVID | | 2 | |
| Stopped treatment – no treatment in at least 3 months | | 65 | |
| **Total** | **254** | **191** | **24** |

[p] Relates to outcomes submitted by the trust in table 11.
[q] Relates to treatment status in table 8 for those that have ended treatment.

## Overall survival (OS)

Of the 814 patients with a treatment record in SACT, the minimum follow-up was five months (152 days) from the last CDF application. Patients were traced for their vital status on 28 April 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 10.8 months (328 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 28 April 2021. The median OS was not reached.

OS at 6 months was 80% [95% CI: 77%, 83%], 12 months OS was 69% [95% CI: 65%, 72%] and OS at 18 months was 61% [95% CI: 57%, 64%].

**Figure 4. Kaplan-Meier survival plot (N=814)**

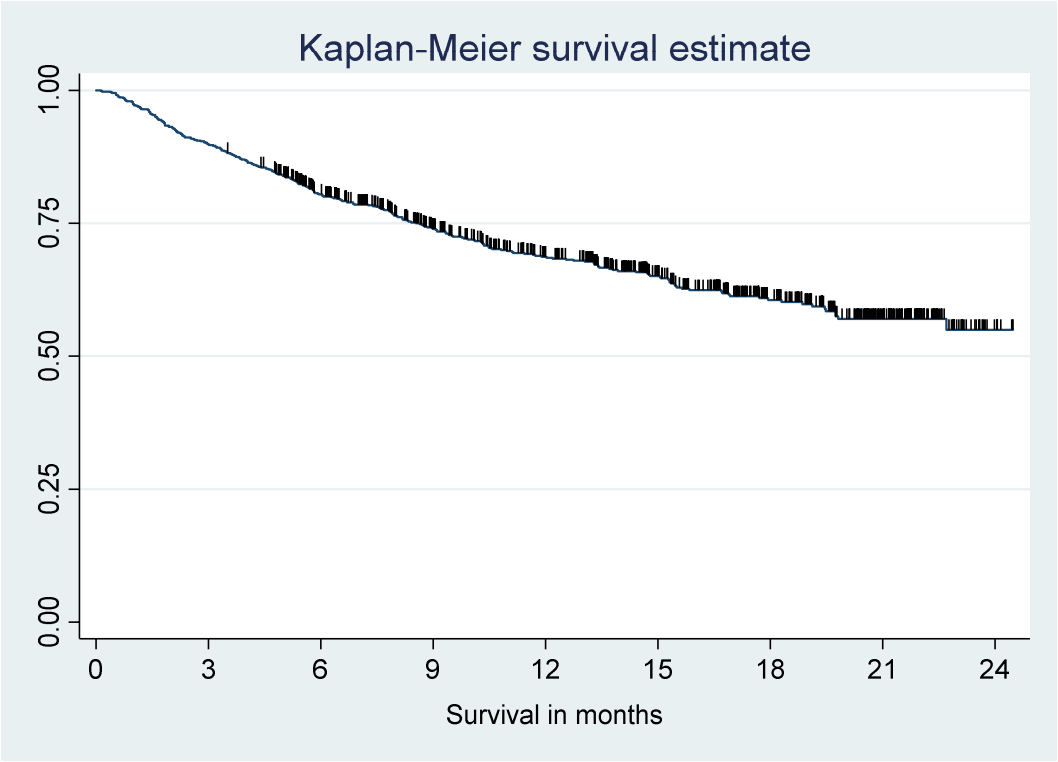



Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 24.7 months (751 days), all patients were traced on 28 April 2021.

**Table 13. Includes the number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 814 | 731 | 605 | 472 | 376 | 277 | 170 | 78 | 3 |

Table 14 shows that for all patients who received treatment, 536 were still alive (censored) at the date of follow-up and 278 had died (events).

**Table 14. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| Censored | 536 | 536 | 485 | 396 | 332 | 251 | 161 | 77 | 3 |
| Events | 278 | 195 | 120 | 76 | 44 | 26 | 9 | 1 | 0 |

# Sensitivity analyses

## 6-month SACT follow up

### Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from between 5 April 2019 and 30 May 2020 in and SACT activity was followed up to the 30 November 2020.

Following the exclusions above, 593 patients (73%) were included in these analyses. The median follow-up time in SACT was 4.3 months (130 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 4.3 months [95% CI: 3.3, 5.5] (130 days) (N=593).

**Figure 5. Kaplan-Meier treatment duration plot (N=593)**

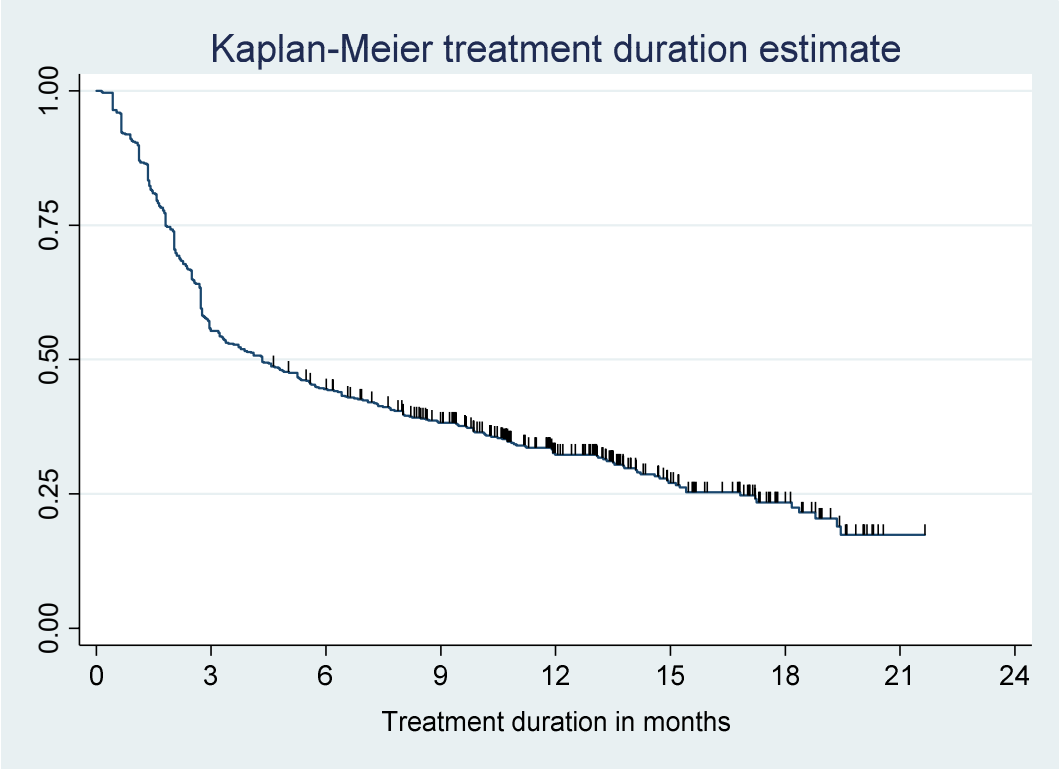



Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19.9 months (605 days).

**Table 15. Includes the number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| Number at risk | 593 | 328 | 259 | 201 | 125 | 64 | 26 | 1 |

Table 16 shows that for all patients who received treatment, 175 were still on treatment (censored) at the date of follow-up and 418 had ended treatment (events).

**Table 16. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| Censored | 175 | 175 | 170 | 147 | 98 | 52 | 21 | 1 |
| Events | 418 | 153 | 89 | 54 | 27 | 12 | 5 | 0 |

## Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 5 April 2019 to 28 October 2020.

Following the exclusions above, 757 patients (93%) were included in these analyses. The median follow-up time in SACT was 11.9 months (362 days).

Figure 6 provides the Kaplan-Meier curve for OS, censored at 28 April 2021. The median OS was not reached.

**Figure 6: Kaplan-Meier survival plot (N=757)**

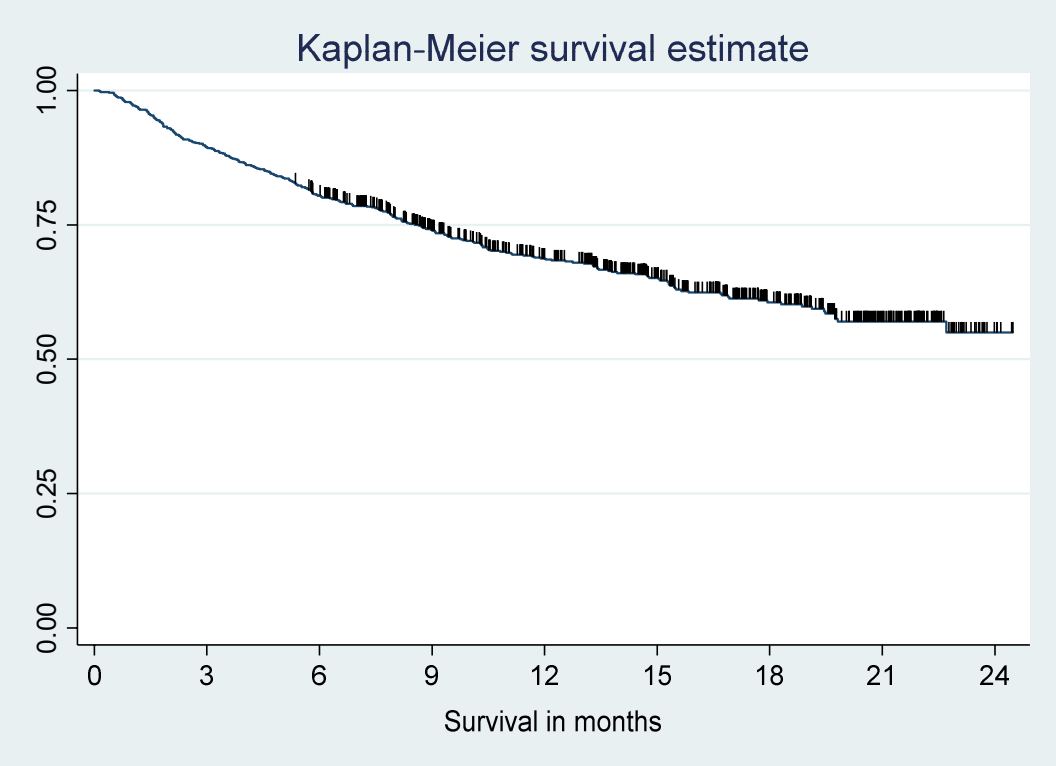



Table 17 and 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 24.7 months (751 days), all patients were traced on 28 April 2021.

**Table 17: Includes the number of patients at risk, by quarterly breakpoints.**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 757 | 677 | 601 | 472 | 376 | 277 | 170 | 78 | 3 |

Table 18 shows that for all patients who received treatment, 489 were still alive (censored) at the date of follow-up and 268 had died (events).

**Table 18: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| Censored | 489 | 489 | 481 | 396 | 332 | 251 | 161 | 77 | 3 |
| Events | 268 | 188 | 120 | 76 | 44 | 26 | 9 | 1 | 0 |

# Secondary sensitivity analyses

## Treatment duration by IMDC progression factors

The median follow-up time in SACT amongst patients who had an IMDC score of 1 or 2 was 3.3 months (100 days). The median follow-up time in SACT amongst patients who had an IMDC score between 3 and 6 was 2.7 months (82 days).

**Table 19: Treatment duration at 6, 12, 18 month intervals**

| Time period | Intermediate risk disease (IMDC score of 1 or 2) | Poor risk disease (IMDC score of 3-6) |
|---|---|---|
| 6 months | 52% [95% CI: 48%, 57%] | 41% [95% CI: 35%, 47%] |
| 12 months | 41% [95% CI: 36%, 46%] | 26% [95% CI: 20%, 32%] |
| 18 months | 29% [95% CI: 23%, 35%] | 19% [95% CI: 13%, 26%] |

The Kaplan-Meier curve by IMDC progression factors is shown in figure 7. The median treatment duration for all patients who had an IMDC score of 1 or 2 was 7 months [95% CI: 5.3, 9.4] (213 days). The median treatment duration for all patients who had an IMDC score between 3 and 6 was 3.3 months [95% CI: 2.7, 4.8] (100 days).

**Figure 7. Kaplan-Meier treatment duration by IMDC factors plot (N=814)**

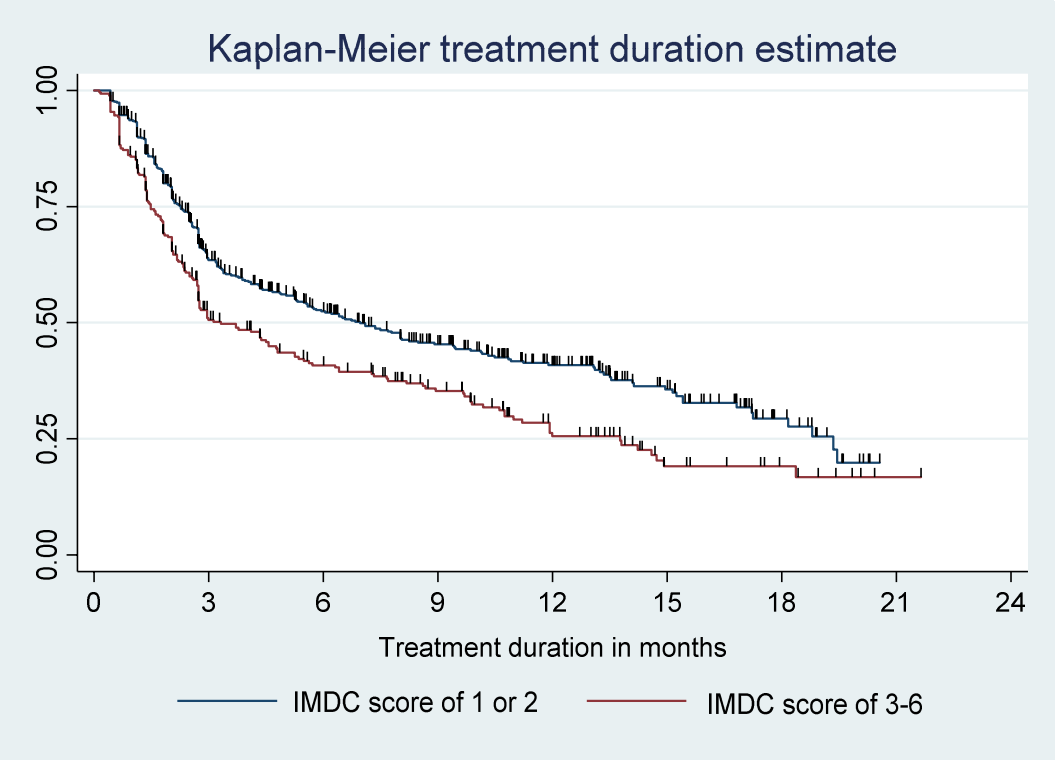



Table 20, 21 and Table 22 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period by IMDC factors. The maximum follow-up period for all patients for treatment duration was 19.9 months (605 days).

**Table 20. Includes the number of patients at risk, by IMDC score and quarterly breakpoints**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| **Number at risk** IMDC score of 1 or 2 | 533 | 276 | 196 | 138 | 91 | 51 | 18 | 0 |
| **Number at risk** IMDC score of 3- 6 | 281 | 119 | 87 | 64 | 35 | 14 | 8 | 1 |

Table 21 shows that for all patients who received treatment and who had an IMDC score of 1 or 2, 251 were still on treatment (censored) at the date of follow-up and 282 had ended treatment (events).

**Table 21: Number of patients at risk amongst patients who have an IMDC score of 1 or 2, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 |
|---|---|---|---|---|---|---|---|
| Censored | 251 | 175 | 140 | 106 | 71 | 40 | 14 |
| Events | 282 | 101 | 56 | 32 | 20 | 11 | 4 |

Table 22 shows that for all patients who received treatment and who had an IMDC score of between 3 and 6, 94 were still on treatment (censored) at the date of follow-up and 187 had ended treatment (events).

**Table 22: Number of patients at risk amongst patients who have an IMDC score of 3-6 by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0-21 | 3-21 | 6-21 | 9-21 | 12-21 | 15-21 | 18-21 | 21 |
|---|---|---|---|---|---|---|---|---|
| Censored | 94 | 64 | 54 | 42 | 28 | 13 | 7 | 1 |
| Events | 187 | 55 | 33 | 22 | 7 | 1 | 1 | 0 |

## Overall survival

Patients were traced for their vital status on 28 April 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT amongst patients who had an IMDC score of 1 or 2 was 12.2 months (371 days). The median follow-up time in SACT amongst patients who had an IMDC score between 3 and 6 was 8.7 months (264 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

**Table 23: OS at 6, 12, 18 month intervals**

| Time period | Intermediate risk disease (IMDC score of 1 or 2) | Poor risk disease (IMDC score of 3-6) |
|---|---|---|
| 6 months | 88% [95% CI: 84%, 90%] | 67% [95% CI: 61%, 72%] |
| 12 months | 76% [95% CI: 72%, 80%] | 55% [95% CI: 49%, 61%] |
| 18 months | 69% [95% CI: 64%, 73%] | 45% [95% CI: 38%, 51%] |

The Kaplan-Meier curve by IMDC progression factors is shown in figure 7. The median OS for all patients who had an IMDC score of 1 or 2 was not reached. The median OS for all patients who had an IMDC score between 3 and 6 was 15 months[r] (456 days).

**Figure 8: Kaplan-Meier survival plot by IMDC factor (N=814)**

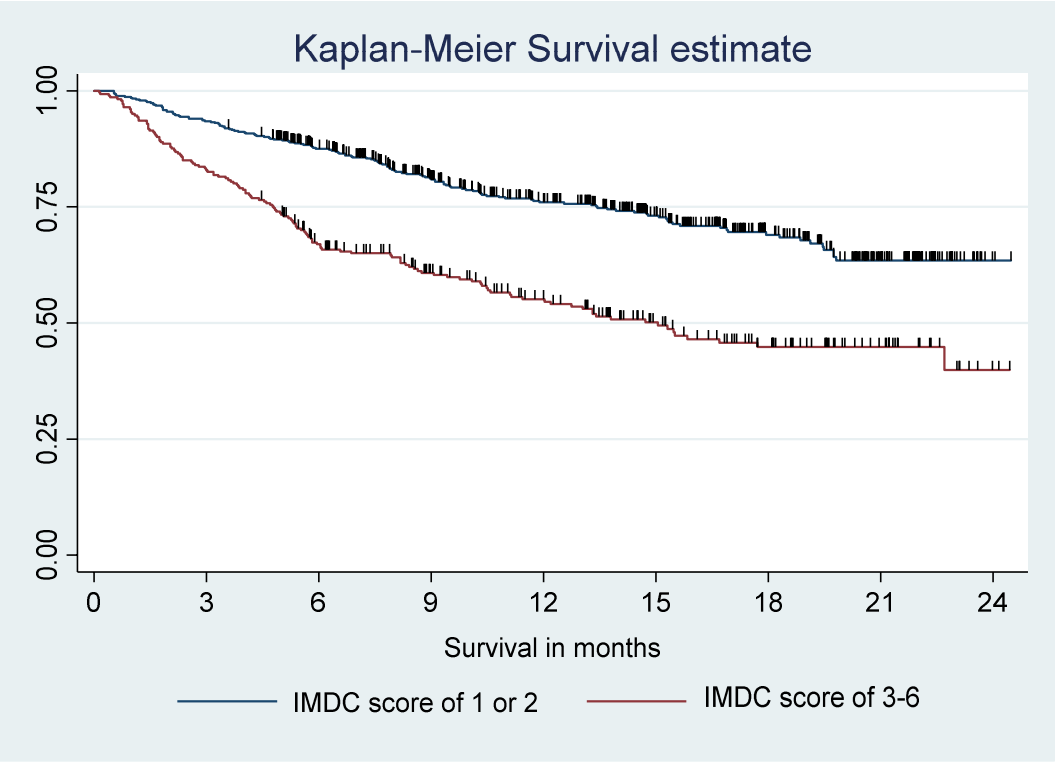



Table 24, 25 and 26 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period by IMDC factors. The maximum follow-up period for survival was 24.7 months (751 days), all patients were traced on 28 April 2021.

[r] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

**Table 24: Includes the number of patients at risk, by IMDC factors and quarterly breakpoints.**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| **Number at risk** IMDC score of 1 or 2 | 533 | 498 | 431 | 337 | 269 | 204 | 204 | 55 | 1 |
| **Number at risk** IMDC score of 3- 6 | 281 | 233 | 174 | 135 | 107 | 73 | 48 | 23 | 2 |

Table 25 shows that for all patients who received treatment and who had an IMDC score of 1 or 2, 391 were still alive (censored) at the date of follow-up and 142 had died (events).

**Table 25: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints amongst patients who have an IMDC score of 1 or 2**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| Censored | 391 | 391 | 355 | 290 | 242 | 186 | 114 | 55 | 1 |
| Events | 142 | 107 | 76 | 47 | 27 | 18 | 8 | 0 | 0 |

Table 26 shows that for all patients who received treatment and who had an IMDC score of 3-6, 145 were still alive (censored) at the date of follow-up and 136 had died (events).

**Table 26: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints amongst patients who have an IMDC score of 3-6**

| Time intervals (months) | 0-24 | 3-24 | 6-24 | 9-24 | 12-24 | 15-24 | 18-24 | 21-24 | 0-24 |
|---|---|---|---|---|---|---|---|---|---|
| Censored | 145 | 145 | 130 | 106 | 90 | 65 | 47 | 22 | 2 |
| Events | 136 | 88 | 44 | 29 | 17 | 8 | 1 | 1 | 0 |

**Table 27. Median treatment duration and OS, full cohort and sensitivity analysis**

| Metric | Standard analysis: Full cohort | Sensitivity analysis: 6 months follow-up cohort: treatment duration | Sensitivity analysis: 6 months follow-up cohort: OS | Secondary sensitivity analysis: IMDC score of 1 or 2 | Secondary sensitivity analysis: IMDC score of 3-6 |
|---|---|---|---|---|---|
| **N** | 814 | 593 | 757 | 533 | 281 |
| **Median treatment duration** | 5.5 months [95% CI: 4.3, 7.0] (167 days) | 4.3 months [95% CI: 3.3, 5.5] (130 days) | | 7.0 months [95% CI: 5.3, 9.4] (213 days) | 3.3 months [95% CI: 2.7, 4.8] (100 days) |
| **OS** | Not reached | | Not reached | Not reached | 15.0 months[s] (456 days). |

[s] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

# Conclusions

820 patients received nivolumab with ipilimumab for the treatment of untreated intermediate or poor risk advanced renal cell carcinoma [TA581] through the CDF in the reporting period (5 April 2019 and 30 November 2020). 814 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional 12 patients with a CDF application did not receive treatment and 25 patients died before treatment, this was confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 73% (N=596) of patients that received nivolumab with ipilimumab for untreated intermediate or poor risk advanced renal cell carcinoma were male, 27% (N=218) of patients were female and most of the cohort were aged between 50 and 79 years of age (85%, N=695).

At data cut off, 58% (N=469) of patients were identified as no longer being on treatment. Of these 469 patients, 27% (N=128) of patients stopped treatment due to progression, 20% (N=94) of patients stopped treatment due to acute toxicity, <1% (N=2) of patients chose to end their treatment, 28% (N=131) of patients died not on treatment, 5% (N=24) of patients died on treatment, 5% (N=23) of patients completed treatment as prescribed, <1% (N=2) of patients stopped treatment due to COVID and 14% (N=65) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration for all patients was 5.5 months [95% CI: 4.3, 7.0] (167 days). 48% of patients were still receiving treatment at 6 months [95% CI: 45%,52%], 35% of patients were still receiving treatment at 12 months [95% CI: 31%, 39%] and 25% of patients were still receiving treatment at 18 months [95% CI: 21%, 30%].

The median OS was not reached. OS at 6 months was 80% [95% CI: 77%, 83%], OS at 12 months was 69% [95% CI: 65%, 72%] and OS at 18 months was 61% [95% CI: 57%, 64%].

Sensitivity analyses were carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed a difference of 1.2 months (full cohort = 5.5 months; sensitivity analysis cohort = 4.3 months) but the difference was not statistically different. Results of OS showed no difference and the median OS was not reached.

A secondary sensitivity analyses was carried out on treatment duration and OS by IMDC score. Results showed a statistically significant difference. Results for treatment duration showed a difference of 3.7 months (IMDC score 1 or 2 = 7.0 months [95% CI: 5.3, 9.4]; IMDC score 3-6 =

3.3 months [95% CI: 2.7, 4.8] OS amongst all patients with an IMDC score of 1 or 2 was not reached. OS amongst all patients with an IMDC score of 3-6 was 15 months[t] (456 days).

# References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7. CheckMate 214 study: 2018 [cited 2021 May] Available from: https://clinicaltrials.gov/ct2/show/NCT02231749

8. Systemic Anti-Cancer Therapy [Internet]: SACT: 2019 [cited 2021 May]. Available from: http://www.chemodataset.nhs.uk/home

9. CDF analytical methods. [Internet]. PHE: 2019 [cited 2021 May]. Available from: http://www.chemodataset.nhs.uk/nhse_partnership/


[t] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

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Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000

Website: www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland



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# Technical engagement response form

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. The NICE technical team have also added a potential key issue.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

Technical engagement response form

NICE National Institute for Health and Care Excellence

# About you

**Table 1 About you**

| | |
|---|---|
| **Your name** | Sophia Ho |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Bristol Myers Squibb |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |

## Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the ERG report or by the NICE technical team.

**Table 2 Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Company overall survival model projections for patients who received NIVO+IPI in the first-line setting do | Yes | BMS reinforce that the company base case is appropriate and supported by clinical data provided in the CDF exit company submission, clinical expert opinion, and additional data provided in this response. BMS reiterate that an equal hazard of death approach is clinically implausible and inappropriate for decision making as it is not based on sufficient clinical evidence, clinical expectation for those patients who are still alive at 5 years in both arms of CheckMate 214 (for whom the overall survival (OS) extrapolations are of relevance), or in line with prior precedent in similar appraisals in aRCC or solid tumour oncology by NICE. Further evidence is provided from CheckMate 214 supporting the long-term survival outcomes of those treated with NIVO+IPI versus sunitinib, in particular evidence for patients for whom the long-term survival |

| | | |
|---|---|---|
| not reflect the CheckMate 214 trial 60-month minimum follow-up overall survival data | | extrapolations are most relevant (i.e. those with an OS of 5 years or more). Additional analyses have been performed to explore validity underpinning the ERGs equal hazard of death scenarios and the plausibility of the company long-term overall survival projections, and are provided herein.<br><br>**Comparison of company base case compared with CheckMate 214 60-month minimum follow-up data**<br>BMS disagree with the interpretation that the company OS projections do not reflect the CheckMate 214 60-month follow-up data. Considering the economic model incorporates the area under the curve in calculations, Kaplan-Meier (KM) data were compared with the company base case over the minimum available follow-up. As shown in Table 1, restricted mean overall survival (OS) over 60 months is [redacted] months for NIVO+IPI and [redacted] months for sunitinib (difference between arms of [redacted] months or more than [redacted] years). When compared to the KM restricted means, the company model extrapolations result in a [redacted] of mean OS for NIVO+IPI and [redacted] of mean OS for sunitinib, both of which are [redacted] in magnitude versus the KM data. Therefore, BMS believe the company survival projections reflect the 60-month data accurately for both arms, and that the extrapolations appropriately reflect the observed OS events to 60 months.<br><br>**Table 1. Comparison of restricted mean OS (area under the curve) to 60 months between CheckMate 214 KM data and company base case extrapolations** |

| | CheckMate 214 KM data (60-month minimum DBL) | | Company base case (independent log-normal) | |
|---|---|---|---|---|
| | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |
| Restricted Mean Survival to 60 months | [redacted] | [redacted] | [redacted] | [redacted] |
| Difference versus KM data | [redacted] | [redacted] | [redacted] | [redacted] |

BMS believe that interpretation of long-term OS projections in the economic model cannot be separated from clinical interpretation of the patients who are, in fact, alive at 60 months, as survival of these patients is what the model predicts over the rest of the model time horizon. Therefore, the OS events just prior to 60 months should not be viewed as more relevant or having greater importance than the clinical status of intermediate/poor risk aRCC patients who are still alive at 5 years. BMS reinforce that patient status will have an influence on longer term survival (i.e. whether at 5 years a patient is progression-free and off therapy, progression-free and still on first-line therapy, still remaining in response, or progressed) and the number of line(s) of therapy received are also essential to inform the OS projections of these patients past 5 years.

**Conditional survival analyses - Patients with overall survival of at least 5 years**

As the 60-month minimum follow-up mark has now been reached, it is now the remaining patients who have survived up until this 5-year timepoint who are subject to extrapolation assumptions as their

| | | |
|---|---|---|
| | | outcomes are still uncertain. In total, there are 163 NIVO+IPI patients and 113 sunitinib patients with an OS of at least 5 years who are considered in this analysis, representing 38.4% and 26.5% of patients from the CheckMate 214 study, respectively.[1]<br>Similar to the 60-month minimum follow-up data previously presented (CS sections A.6.1.2, response to clarification question B1), NIVO+IPI patients with an OS of at least 5 years are continuing to benefit from their first-line treatment, as the median duration of response (DoR) still has not been met for NIVO+IPI compared with 23.5 months (95% CI: 18.2-60.4 months) with sunitinib (see Figure 1) and among responders who have an OS of 5 years or more, 75.0% of NIVO+IPI patients have a durable response of at least 60 months compared with 38.0% of patients in the sunitinib arm (see Table 3). The higher proportion of patients responding to treatment is also reflected in Figure 2 where 71.3% of patients who are alive at 5 years had a tumour reduction greater than or equal to 50%, whereas in the sunitinib arm 37.0% of patients experience such a reduction.<br>Consistent with the 60-month data cut presented in the company submission for intermediate-/poor- risk patients in CheckMate 214, patients with an OS of at least 5 years continue to demonstrate a substantial improvement in PFS compared with patients treated with sunitinib. The HR has improved from [redacted] with all patients regardless of OS, to HR [redacted], meaning patients in the NIVO+IPI arm who have an OS of 5 years or more have a 65% reduction in the risk of progression versus those who received sunitinib and are alive at 5 years. In patients alive at 5 years, the [redacted] with NIVO+IPI as [redacted] of patients remain progression-free, which is [redacted] |

[redacted] of sunitinib patients ([redacted])of sunitinib patients and a median PFS of [redacted] months (HR [redacted]) (see Table 2 and Figure 3). More specifically, when considering the patients who experienced a response (either a complete response (CR) or a partial response (PR)) as their best overall response (representing 70.6% of NIVO+IPI patients versus 50.0% of sunitinib patients alive at 5 years), [redacted] and [redacted] of NIVO+IPI and sunitinib patients remain progression-free, respectively (see Table 2). This data demonstrates that patients who achieve an objective response with NIVO+IPI are more likely to achieve clinically relevant benefits in terms of PFS benefits sustained with longer follow-up than patients who achieve a response with sunitinib (see Table 4), which is in line with clinical expert expectations in relation to for NIVO+IPI where given the PFS plateau, the PFS curve would eventually meet the OS curve, as a proportion of patients are expected to not have disease progression before death.[2].

**Table 2 Best overall response per IRRC and progression events per IRRC (secondary definition) for patients with OS at least 5 years, intermediate/poor risk patients**

| | Number of subjects n (%) | | Number of progression events per IRRC (secondary definition) n (%) | |
|---|---|---|---|---|
| | NIVO+IPI (n = 425) | Sunitinib (n = 422) | NIVO+IPI (n = 425) | Sunitinib (n = 422) |
| Patients with OS at least 5 years | 163 | 112 | 163 | 112 |
| Complete response (CR) | 40 (24.5) | 7 (6.3) | [redacted] | [redacted] |
| Partial response (PR) | 75 (46.0) | 49 (43.8) | [redacted] | [redacted] |

| | | | | | |
|---|---|---|---|---|---|
| Stable disease / non-CR / non-PD | 40 (24.5) | 38 (33.9) | [redacted] | [redacted] |
| Progressive disease (PD) | 7 (4.3) | 14 (12.5) | [redacted] | [redacted] |
| Unable to determine (UTD) | 1 (0.6) | 3 (2.7) | [redacted] | [redacted] |
| Not reported | 0 | 1 (0.9) | [redacted] | [redacted] |

**Table 3 Proportion of patients with DoR over different timepoints, intermediate/poor risk patients with OS at least 5 years from CheckMate 214**

| | Duration of response of at least (95% CI) | |
|---|---|---|
| | NIVO+IPI (n = 163) | Sunitinib (n = 112) |
| 24 months | [redacted] | [redacted] |
| 30 months | [redacted] | [redacted] |
| 36 months | [redacted] | [redacted] |
| 42 months | [redacted] | [redacted] |
| 48 months | [redacted] | [redacted] |
| 60 months | [redacted] | [redacted] |

**Table 4 PFS rate per IRRC (secondary definition) over different timepoints, intermediate/poor risk patients with OS at least 5 years from CheckMate 214**

| | PFS rate (95% CI) | |
|---|---|---|
| Median PFS | NIVO+IPI (n = 163) | Sunitinib (n = 112) |
| 12 months | [redacted] | [redacted] |
| 24 months | [redacted] | [redacted] |
| 36 months | [redacted] | [redacted] |
| 48 months | [redacted] | [redacted] |
| 60 months | [redacted] | [redacted] |

| | | |
|---|---|---|
| | | As per the original company submission (TA581) and CDF review submission, the same criteria of including systemic therapies received by 5% or more patients in either arm at any time during the trial was applied in the economic model. Amongst patients with OS of at least 5 years, subsequent treatments received in the NIVO+IPI arm were almost half of that in the NIVO+IPI arm (39.3% versus 75.0%). This is further supported by the swimmer plots presented in the company submission (figure 53 and figure 54 of the CDF review company submission) demonstrating that amongst patients with an objective response (PR or CR) as their best overall response, [redacted] of NIVO+IPI patients are off treatment and have never received subsequent therapy versus [redacted] of patients in the sunitinib arm. These observations are in line with clinical expectations who expect a greater proportion of NIVO+IPI patients to not receive subsequent treatment because they do not need to, as they are still receiving clinical benefit from the long-term effects of NIVO+IPI, referencing the tail of the PFS curve where patients do not need any more treatment.[2]<br><br>**Evidence from CheckMate 214 60-month minimum follow-up**<br>BMS have previously provided a number of clinical outcomes in the company submission and response to clarification questions, for brevity they are not included here and BMS request that these continue to be considered in relation to the OS extrapolations.<br>NIVO+IPI patients who achieve a response (CR or PR) have improved post-response survival compared with sunitinib (HR [redacted]), with [redacted] that is |

[redacted] the follow-up period (see Figure 4). This data demonstrates that NIVO+IPI patients who respond have improved OS over sunitinib patients. The improved post-response survival with NIVO+IPI is also in line with clinical expert expectations where patients who experience a durable response would be expected to achieve long-term survivorship, and that nivolumab monotherapy would be less effective at providing this long-term response than NIVO+IPI.[2] Considering that the proportion of patients still alive at 5 years and achieve response (as demonstrated above) is higher for NIVO+IPI, it would be clinically inappropriate to assume the risk of death would be equal to that of sunitinib.

The restricted mean survival time (RMST) for PFS per IRRC by secondary definition, time from randomization to first subsequent systemic anticancer therapy, second systemic anticancer therapy and OS is presented in Table 5. With increasing time, the benefits, as demonstrated by area under the KM curves, of the aforementioned endpoints increase between NIVO+IPI and sunitinib. Moreover, with a minimum follow-up of 60-months in CheckMate 214, NIVO+IPI has demonstrated an extension of [redacted] mean months to progression, [redacted] mean months to first subsequent treatment, [redacted] mean months to second subsequent treatment and [redacted] mean months extension to OS compared with the sunitinib.

**Table 5 Restricted mean survival time, intermediate/poor risk patients (minimum 60-month follow-up)**

| | NIVO+IPI (n = 425) | Sunitinib (n=422) | Difference (95%CI) | Ratio, NIVO+IPI versus Sunitinib (95% CI) |
|---|---|---|---|---|
| | PFS per IRRC, secondary definition | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | Time from Randomization to First Subsequent Systemic Anticancer Therapy | | | |
| | | 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | Time from Randomization to Second Subsequent Systemic Anticancer Therapy | | | |
| | | 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | OS | | | |
| | | 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | Key: CI, confidence interval; RMST, restricted mean survival time. | | | |

| | | |
|---|---|---|
| | | If the ERG's position that the survival benefit of NIVO+IPI diminishes from approximately 54 months were to be supported by the data from CheckMate 214, this would be reflected in a diminishing treatment effect after RECIST progression when patients go on to receive further subsequent lines of therapy. This can be captured by evaluating time from randomisation to second objective disease progression (PFS2), which can show whether randomised therapy has a negative effect on the efficacy of second-line treatment received after disease progression. The CheckMate 214 study did not include PFS2 as a secondary endpoint because RECIST data were not collected for subsequent therapies. However, it was possible to evaluate the exploratory endpoint of time from randomisation to second subsequent therapy or death (TSST) as a proxy for PFS2, recognizing that some patients may discontinue treatment before initiating a further line of therapy. We also evaluated time from randomisation to first subsequent therapy (TFST) which is often considered to be a proxy for symptomatic disease progression on randomised therapy in cancer RCTs.<br>The KM plots of TFST and TSST from the CheckMate 214 60-month minimum follow-up are presented in Figure 5 and Figure 6 and a summary of the median and HR estimates (with 95% CIs) are provided in Table 6. It is apparent in the plot of TSST that treatment benefit with NIVO+IPI is [redacted], [redacted] on the efficacy of subsequent therapy, which further highlights the durability of treatment benefit, with a HR of [redacted] and a gain in median TSST of [redacted] months versus sunitinib (median TSST: [redacted] versus [redacted]. This is despite a significant proportion of sunitinib patients ([redacted]) being treated |

with nivolumab as a subsequent therapy post-progression. Similarly, NIVO+IPI patients experienced [redacted]TFST, with a HR of [redacted]) and a gain in median TFST of [redacted] months versus sunitinib (median TFST: [redacted] versus [redacted], respectively). It is also worth noting that, considering a proportion of patients still alive in the NIVO+IPI arm are still on first-line therapy when patients in the sunitinib arm are receiving subsequent nivolumab, the progression of disease is also of relevance in influencing OS. BMS reiterate that patients who have progressed on 1L sunitinib and receive nivolumab as 2L or 3L monotherapy experience worsening of their disease; therefore, any direct comparison of longer term survival of patients who have progressed and receive subsequent therapy with a first-line patient who is either in response or stable disease would be inappropriate.

**Table 6 Summary statistics for TFST and TSST by treatment – CheckMate 214 intermediate/poor risks patients (60-month minimum follow-up)**

| Endpoint | Treatment | N | Events | Censors | Median (m; 95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|
| TFST | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |
| | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |
| TSST | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |
| | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |

Key: TFST, time to first subsequent systematic anti-cancer therapy; TSST, time to second subsequent systematic anti-cancer therapy; CI, confidence interval, HR, hazard ratio; m, month; n, number.

**Table 7 Subsequent treatment split by treatment arm from CheckMate 214 intermediate/poor risk patients with OS of at least 5 years**

| | NIVO+IPI (n = 163) | | Sunitinib (n = 112) | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients who received systemic subsequent treatment | 64 | 39.3 | 84 | 75.0 |
| Nivolumab | 17 | 10.4 | 59 | 52.7 |
| Axitinib | 22 | 13.5 | 28 | 25.0 |
| Cabozantinib | 27 | 16.6 | 26 | 23.2 |
| Everolimus | [redacted] | [redacted] | [redacted] | [redacted] |
| Pazopanib | 19 | 11.7 | 6 | 5.4 |
| Sunitinib | 24 | 14.7 | 15 | 13.4 |
| Investigational antineoplastic | [redacted] | [redacted] | [redacted] | [redacted] |

**Mortality rates using alternative time intervals.**

The ERG have based their equal hazard of death assumption on annual mortality rates from CheckMate 214, including OS rates for when less than 5 patients are at risk in either arm (i.e. 6 years or 72 months). BMS challenge the appropriateness of this approach in using what seems to be an arbitrary time point versus leveraging individual patient level data and event times, as this annual OS rate method is not established in NICE DSU guidance documents for survival extrapolation.[3] In addition, when looking at the

| | | |
|---|---|---|
| | | mortality rate over differing intervals other than the 12-month interval chosen by the ERG, the trend of the mortality rate is [redacted] NIVO+IPI versus sunitinib, [redacted] instances where the death rate is [redacted] for sunitinib; however, this trend is not consistent across intervals chosen for examination. As can be seen in Table 8 and Table 9, the selection of time interval when assessing the mortality rate impacts the ability to derive conclusions on the hazard between the rates of NIVO+IPI and sunitinib. BMS reiterate that this is an inappropriate method of justification, subject to bias and should not be used to justify the use of an equal hazard between NIVO+IPI and sunitinib in absence of consideration of the clinical status of patients still alive at 5 years in both treatment arms. It should also be noted that amongst the patients who have OS of at least 5 years who are subject to the ERG's equal hazard of death assumption, [redacted] of NIVO+IPI patients are still progression-free compared with [redacted] in the sunitinib arm. Acceptance of an equal hazard of death assumption from 4.5 years would be analogous to accepting an assumption that patients who are on first-line therapy and those who are still responding (and may be free of disease, noting the proportion of patients alive at CR who have achieved and are still in CR), have the same risk of death as a patient who may be on his or her second-, third-, fourth- or later line of therapy. BMS reinforce that annual OS rates are not an established methodology and should not be considered justification or validation of an equal hazard of death assumption and that only clinically plausible assumptions should be considered appropriate for decision making, in line with the current draft proposed NICE new methods guidance.[4] |

**Table 8 CheckMate 214 mortality rates over alternative time intervals - intermediate/poor risk (3, 6, 9 and 18 months)**

| | 3 months | | 6 months | | 9 months | | 18 months | |
|---|---|---|---|---|---|---|---|---|
| | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |
| 0 to 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 to 6 | [redacted] | [redacted] | | | | | | |
| 6 to 9 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 9 to 12 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| 12 to 15 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 15 to 18 | [redacted] | [redacted] | | | | | | |
| 18 to 21 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 21 to 24 | [redacted] | [redacted] | | | | | | |
| 24 to 27 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 27 to 30 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| 30 to 33 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 33 to 36 | [redacted] | [redacted] | | | | | | |
| 36 to 39 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 39 to 42 | [redacted] | [redacted] | | | | | | |
| 42 to 45 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 45 to 48 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| 48 to 51 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 51 to 54 | [redacted] | [redacted] | | | | | | |
| 54 to 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 57 to 60 | [redacted] | [redacted] | | | [redacted] | [redacted] | [redacted] | [redacted] |

* - Asterix to denote occasions where the mortality rate is greater for NIVO+IPI than sunitinib

**Table 9 CheckMate 214 mortality rates over alternative time intervals - intermediate/poor risk (24 months)**

| | NIVO+IPI | Sunitinib |
|---|---|---|
| **0 to 24** | [redacted] | [redacted] |
| **12 to 36** | [redacted] | [redacted] |
| **24 to 48** | [redacted] | [redacted] |
| **36 to 60** | [redacted] | [redacted] |

**The ERG's preferred modelling of overall survival does not adequately reflect the CheckMate 214 60-month minimum follow-up OS data**

The company notes that the ERG did not provide a visual assessment of the modelled OS from their preferred scenarios, which applied equal mortality hazards for the treatment arms from 54 months onwards. When implementing this in the company model, it was clear that the ERG's scenario leads to significant changes in long-term extrapolations, especially to the NIVO+IPI arm as a result of the assumption of equal mortality hazards with sunitinib being applied from 54 months (see Figure 7). The company maintain that the base case OS modelling based on the log-normal distribution adequately reflects the observed trial data to the minimum 60-month follow-up and the long-term projections past 5 years may in fact be conservative for NIVO+IPI, considering the clinical data presented and clinical status of patients alive in both arms at 5 years. This is further reflected in a comparison of RMST to 60-months follow-up from the CheckMate 214 trial and the company's base case model as presented in Table 1.

| | | |
|---|---|---|
| | | **Plausibility of company long-term overall survival projections**<br>When selecting appropriate extrapolations, investigation of visual fit to smoothed hazards is considered in addition to statistical fit criteria and clinical plausibility. In the case of CheckMate 214, an artificial upward trend is observed in the smoothed hazard plots for NIVO+IPI in the 60-month DBL starting at an earlier time point that contrasts with prior data cuts. Therefore, we have investigated this further to determine whether this was in fact a true difference in hazard pattern that should be considered or was an artefact of the methodology and unlikely to be truly reflective of the hazards for NIVO+IPI. As shown in the company response to clarification questions (Figure 2, left panel), with both database locks plotted to only 48 months of follow-up, the 60-month minimum DBL smoothed hazard plots [redacted] with the 48-month minimum DBL hazard data, with [redacted] for either treatment arm between DBLs. However, when plotting the 60-month minimum DBL to 60 months (Figure 2, right panel, in company response to clarification questions), the smoothed hazard [redacted] of the 48-month minimum DBL for both treatment arms (NIVO+IPI and SUN) from before 40 months. This [redacted] from the 48-month minimum DBL smoothed hazards demonstrates that information from later in the curve (past the point of minimum follow-up in the prior DBL), and the smoothing hazard function, have an impact on the appearance of the smoothed hazard, [redacted] (i.e., data earlier than the minimum follow-up from the previous DBL). Therefore, it is important to investigate [redacted] to clarify whether this [redacted]. |

| | | |
|---|---|---|
| | | The ERG have stated in their report (section 4.1, p. 26), "*However, as a minimum of 60 months follow-up data are available from the CheckMate 214 trial, there is no censoring before Month 60 and so the unsmoothed hazard rates between Month 48 and Month 60 are completely unaffected by censoring.*" BMS disagree that the unsmoothed hazards are unaffected to the point of minimum follow-up, and have provided plots of the unsmoothed hazards in Figure 3 of the company response to clarification questions. This figure clearly shows that the unsmoothed hazards at the bottom of the figure for the 60-month minimum DBL (blue dashed line) [redacted] the unsmoothed hazard from the 48-month minimum DBL (yellow dashed line) up to the point of minimum follow-up for the 48-month DBL. After this point of 48 months, after which many patients are censored in both treatment arms, the yellow spikes of unsmoothed hazards from the 48-month minimum DBL can be [redacted] from the blue unsmoothed hazards from the 60-month minimum DBL for both NIVO+IPI (left panel) and SUN (right panel). In addition, where the yellow spikes are observed for both panels, it is clear the blue hazard is not experiencing high spikes for either treatment arm after 48 months until after 60 months (i.e. the minimum follow-up from the 60-month DBL).<br>In contrast, **smoothed hazards** can be affected by censoring and differing lengths of included follow-up, as shown in Figure 2 in the company response to clarification questions, and demonstrated below in Figure 8, Figure 9 and Figure 10. To further demonstrate the impact and influence of 1 month of additional included follow-up on the smoothed hazard plot, additional plots were produced whereby all patients in the 48- and 60-month minimum DBLs were censored at a specific time point, which was varied by 1 month |

| | | |
|---|---|---|
| | | from 48 months to 60 months of follow-up (Figure 8). As highlighted by the circles in each panel within the figure, the tails of the hazards vary for both DBLs with just one additional month of data for both treatment arms. The ERG believes that the hazard should be set as equal between treatment arms from 54 months; however, the smoothed hazards for data censored from [redacted] months do not support this assumption in Figure 8. As described above, a change in pattern in the 60-month smoothed hazard plot is observed where both arms [redacted] from the 48-month minimum follow-up at an earlier time point than the minimum follow-up (i.e. 40 months or earlier), which demonstrates that this deviation and pattern is an artefact and should not be used for decision making as this may be resolved with longer trial follow-up, as demonstrated in Figure 9, and Figure 10 below. Figure 9 presents the OS smoothed hazard plots (12-month smoothing interval) along with the corresponding OS KM data published for CheckMate 214 across the DBLs, namely the 30-month minimum, 42-month minimum, 48-month minimum, and 60-month minimum DBLs, while Figure 10 presents these smoothed hazards for the four DBLs overlaid in a single plot.<br><br>**Equal hazard of death plausibility over the long-term**<br>To further investigate the plausibility of the ERG's position that mortality hazards for patients in the NIVO+IPI and sunitinib arms should be set equal from 54 months onwards, an additional analysis was performed to understand at what point parametric hazards cross, which would correspond to an equal hazard of death time point over a 15-year horizon. |

| | | |
|---|---|---|
| | | First, the parameter estimates and the variance-covariance matrix were used to generate 50,000 bootstrapped log hazard rate samples over the 15-year horizon for both NIVO+IPI and sunitinib. Second, the OS time-varying HRs for NIVO+IPI versus sunitinib were estimated by calculating the exponentiated difference in the log hazard rates between the bootstrapped log hazard rate samples. As a result, the median, 2.5%, and 97.5% quantile hazard ratio estimates over time are plotted in Figure 11. All analyses were conducted in R using the flexsurv package[5].<br><br>As shown in Figure 11 in this figure that the median HR of the two models [redacted] and [redacted]. Further, while the 95% CI of the hazard ratio is initially very wide, it gets narrower around [redacted] and from month [redacted]. The percentage of simulations (i.e. the probability) during the 180 month horizon that resulted in an OS HR > 1 for NIVO+IPI versus sunitinib were calculated. Overall, these analyses showed that at 54 months, the percentage of simulations where the HR of NIVO+IPI vs. sunitinib was ≥1 was [redacted]. Furthermore, between [redacted] months, the percentage of simulations with a HR ≥1 reached a maximum of [redacted], indicating an [redacted] of equal hazards between NIVO+IPI and sunitinib over 15-years, based on the available follow-up in CheckMate 214.<br><br>**Precedent from previous NICE appraisal of IO therapies in aRCC**<br>Further to this, BMS would argue that, if the Committee were to agree with the ERG's suggestion of equalising the model mortality hazards for patients in the NIVO+IPI and sunitinib arms from 54 months |

| | | |
|---|---|---|
| | | onwards, this would be inconsistent with previous Committee positions on IO based therapies in aRCC in terms of durability of treatment effect and its relationship with a maximum treatment duration in the trial (treatment stopping rule). The CheckMate 214 trial and the marketing authorisation for NIVO+IPI in untreated intermediate/poor risk aRCC does not apply stopping rules for nivolumab and consequently the Committee concluded that no stopping rules should be applied in the cost-effectiveness model.<br><br>For example, in the appraisal of pembrolizumab plus axitinib for untreated aRCC, which is based on a 2-year stopping rule applied to the pembrolizumab arm in the KEYNOTE-426 study, the committee noted that in previous NICE appraisals of checkpoint inhibitors when length of treatment was capped at 2 years in the cost-effectiveness model, the committee did not assume lifetime treatment benefit but examined various analyses of treatment benefit waning effects.). The committee agreed that there would likely be a durable response from immunotherapy but concluded that there was insufficient evidence to assume this would be lifelong. The committee considered model scenarios when the treatment effect of pembrolizumab stopped after 3 years, 5 years and 10 years (that is, treatment effect continued to 1 year, 3 years and 8 years after stopping pembrolizumab). Although the committee concluded that the immaturity of the data from KEYNOTE-426 (approximately 20 months follow-up) made any estimation of treatment waning effect highly uncertain, it accepted scenarios when a waning effect was applied after 5 years [TA 650 FAD sections 3.10-3.11]. [6] |

| | | |
|---|---|---|
| | | Conversely, in the appraisal of avelumab plus axitinib for untreated aRCC, based on clinical evidence from the JAVELIN Renal 101 trial, which has no maximum treatment duration, the committee concluded that there was no clinical evidence to support a stopping rule and that it should not be in the model. The committee concluded that there was no evidence to support what proportion of patients would have a long-term treatment effect after stopping treatment. Therefore, the modelling should have accounted for a range of potential options, including the potential for no patients to have a long-term treatment effect after stopping treatment. The committee was aware that the company's final model had removed the stopping rule, so the model also excluded treatment waning (that is, because treatment now continued in the model, as aligned with the trial, there was no need to apply assumptions around what happens to the treatment effect after stopping treatment at a set time period, rather than for adverse events or progression). The committee agreed that this approach was appropriate. [TA645 FAD Sections 3.16-3.17].[7]<br><br>It is worth noting that approaches in other solid tumor TAs have also considered a lasting effect of nivolumab after cessation, based on long-term evidence, whereby the committee agreed that the effect, while uncertain, likely lasted "at least three years". In addition, in [redacted].<br><br>Based on the latest 60-month DBL, [redacted] patients in the NIVO+IPI arm were still receiving nivolumab treatment at 54 months and the model (based on the best-fitting [redacted]) further projected that |

| | | |
|---|---|---|
| | | nearly all patients (i.e. just above 99%) in the NIVO+IPI arm would complete their treatment by approximately [redacted] years follow-up. In contrast, approximately [redacted] of patients in the sunitinib arm were still on randomised treatment at 54 months. In addition, approximately [redacted] of patients were still progression-free in the NIVO+IPI arm versus [redacted] in the SUN arm. The company would therefore consider it would be inappropriate to assume equal mortality hazards for N+I versus sunitinib after 54 months [redacted] BMS consider that any assuming impact on mortality hazards between NIVO+IPI and sunitinib prior to all patients completing treatment (with nivolumab) is in contrast with prior solid tumour assessments of immunological therapies, where treatment waning has been considered and/or included in the final base case. |
| Fewer poor-risk patients in the CheckMate 214 trial than in the SACT dataset (21% vs 35%, respectively) | Yes | BMS would like to reiterate that the difference in proportions of intermediate and poor risk patients in CheckMate 214 was resolved in in the original appraisal (TA581) and that "The committee concluded that the combined intermediate- or poor risk group is appropriate for decision making.".<br><br>The ERG stated in their report that a difference in ratio of intermediate and poor risk patients "*only matters if there are differential outcomes and costs for these two groups of patients*". The CheckMate 214 study was not powered for analyses by subpopulations. However, a formal interaction test was conducted for OS and on PFS as assessed by IRRC (secondary definition) on the February 2021 (60-month minimum) data |

| | | |
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| | | cut to further explore potential treatment heterogeneity in the pre-specified subgroups. From this interaction test, a p-value of <0.05 would indicate statistically significant “proof of different effects”.<br><br>For the purposes of displaying baseline characteristics, subgroups are retrieved from the Case Report Form (CRF) as this reflects the true patient population. For stratified analyses, stratification factors are based on data from IRT (Interactive Response Technology) collected at the time of the randomization. Therefore, the HR presented in the tables below for ‘overall’ (i.e. unstratified but intermediate/poor risk combined) differs from that presented in stratified analyses.<br><br>**IMDC risk score**<br><br>On the February 2021 (60-month minimum) data cut, an unstratified cox proportional hazard model was used to assess the significance of the interaction between the treatments and the subgroup based on IMDC intermediate risk score (1-2) or IMDC poor risk score (3-6) (excluding any patient with favourable risk). The unstratified cox proportional hazard model is based on treatment + IMDC + treatment*IMDC. In Table 10, the p-value for the test of interaction is [redacted]; HR are similar and favouring the N+I treatment arm in both subgroups with [redacted] of a quantitative or qualitative interaction between the treatment effect and the baseline IMDC prognostic score (i.e. poor and intermediate subjects) for OS.<br><br>**Table 10 Subgroup analyses of overall survival from the CheckMate 214 study – IMDC risk score (minimum follow-up: 60 months)** |

| | | |
|---|---|---|
| | | [redacted] |

CheckMate 214 February 2021 (60-months minimum) DBL, CI=confidence interval; CRF=case report form; HR = hazard ratio; KME=Kaplan-Meier estimate; N.A.=not available.
(1) KME of median time to event.
(2) Unstratified Cox proportional hazard model. HR is NIVO+IPI over Sunitinib
(3) Unstratified Log-rank Test
(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup

Similar exploratory analysis of PFS (per IRRC, secondary definition) also showed consistent benefit for nivolumab + ipilimumab over sunitinib in the baseline IMDC prognostic score (i.e. poor and intermediate subjects) subgroups with [redacted] of a qualitative or quantitative interaction in this subgroup (p-value for interaction = [redacted];Table 11).

**Table 11 Subgroup analyses of progression-free survival (per IRRC, secondary definition) from the CheckMate 214 study – IMDC risk score (minimum follow-up: 60 months)**

| | | |
|---|---|---|
| | | [redacted] |

CheckMate 214 February 2021 (60-months minimum) DBL, CI=confidence interval; CRF=case report form; HR = hazard ratio; KME=Kaplan-Meier estimate; N.A.=not available.
(1) KME of median time to event.
(2) Unstratified Cox proportional hazard model. HR is NIVO+IPI over Sunitinib
(3) Unstratified Log-rank Test
(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup

In intermediate/poor-risk subjects, OS favoured the NIVO+IPI group vs. the sunitinib group in all pre-defined subgroups. The IMDC risk subgroup analyses based on February 2021 DBL presented here confirmed that finding. There was [redacted] for qualitative or quantitative interactions between treatment and IMDC status (intermediate/poor). The exploratory analyses show that OS was significantly favoured in

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| | | the NIVO+IPI group compared to the sunitinib group, regardless of IMDC risk score, as demonstrated by the difference in median time to event between arms and HRs.<br><br>Given that there is [redacted] of quantitative or qualitative interaction for either subgroup for OS and for PFS per IRRC (secondary definition) as described above, the results from CheckMate 214 for the combined intermediate-/poor-risk patient population are appropriate for assessment within this submission. The lack of proof of indication of different effects, combined with the fact the study was not powered to test outcomes for each risk group separately, demonstrates that the combined population is appropriate.<br><br>**COVID-19 and the impact on SACT**<br>The collection of SACT data could have been impacted by the COVID-19 pandemic, as seen in the retrospective analysis of one of the largest referral centres in the UK; the Specialist Centre for Kidney Cancer at the Royal Free London NHS Foundation Trust.[8] This study demonstrated that during the first surge of the COVID-19 pandemic, diagnosis, referral and treatment of kidney cancer were severely impacted, seeing 2-week wait referrals decreasing by 50%, and the total number of patients discussed at specialist MDT meetings decreasing by 47%, despite the metastatic specialist MDT meetings remaining stable.[8]<br><br>In addition, an online survey of 41 clinical experts with experience treating metastatic clear cell RCC were questioned on treatment decisions outside and during the COVID-19 pandemic and the modifications of systemic therapy implemented.[9] Of the respondents, 71% of responded were clinical experts based in |

| | | |
|---|---|---|
| | | Europe. The majority of clinicians agreed that the IMDC risk score combined with a patients' fitness were considered relevant for factors for decision making. When comparing treatment options amongst fit, intermediate-/poor risk patient, the survey found that over 80% of clinicians would prescribe NIVO+IPI outside of the pandemic, however the pandemic resulted in a statistically significant decrease in the proportion of clinicians who would prescribe NIVO+IPI to 41%, with a third of clinicians preferring to prescribe a TKI. For those patients who are both unfit with an intermediate-/poor- risk, there was no significant change in treatment recommendations before or during the pandemic. The results of the online survey demonstrates that treatment modifications amongst fit, intermediate-/poor risk patients away from NIVO+IPI to a TKI during the pandemic would result in a greater proportion of unfit, intermediate-/poor risk patients being treated with NIVO+IPI.<br><br>Therefore, based on the above, BMS reiterate that the SACT data are not likely to be appropriate for determining the ratio of intermediate/poor risk patients treated in the NHS. In addition to limitations of the SACT data, which has less than 6 months of minimum follow-up, and the time of collection (during the COVID-19 pandemic), the lack of proof of difference of effects between the subgroups reinforces the conclusions of the committee in the original CS that the combined intermediate/poor risk population from CheckMate 214 is appropriate for evaluation of the cost-effectiveness of NIVO+IPI versus sunitinib in this assessment. |

| | | |
|---|---|---|
| Subsequent therapy use varies between CheckMate-214 and SACT | No | BMS has no objection with the ERG position that subsequent treatments from CheckMate 214 is the most appropriate source of information. |

**Figure 1 KM curve of DOR, per IRRC - CheckMate 214 intermediate/poor risk patients with OS of at least 5 years with confirmed objective response[1]**

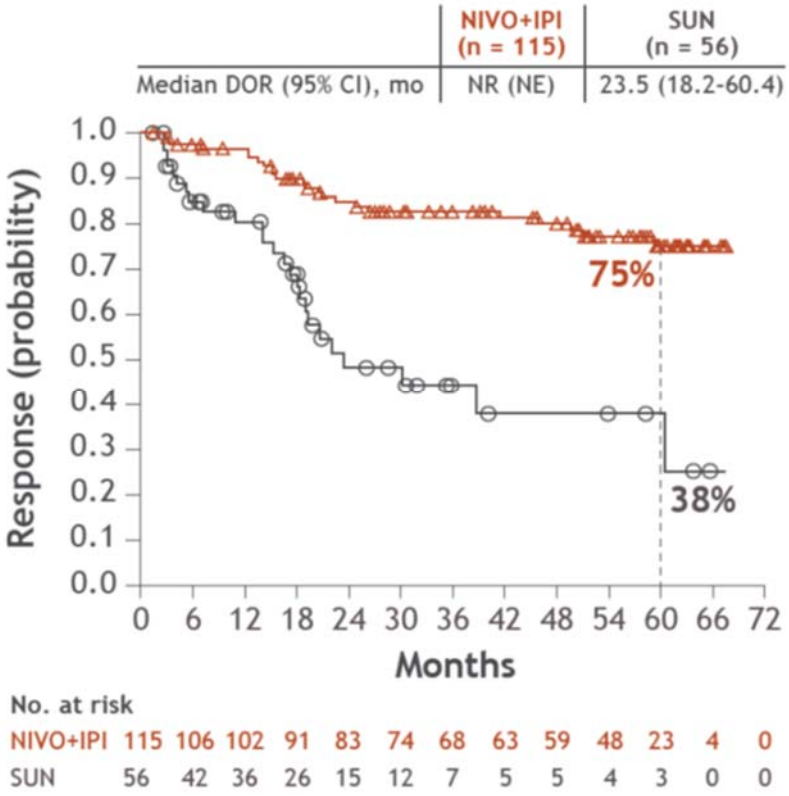


**Figure 2 Waterfall plot of best % reduction from baseline in sum of diameter of target lesions, IRRC - CheckMate 214 intermediate/poor risk patients with OS of at least 5 years**

**Figure 3 KM curve of PFS per IRRC, Secondary definition - All randomised subjects with OS at least 5 years with intermediate/poor risk**

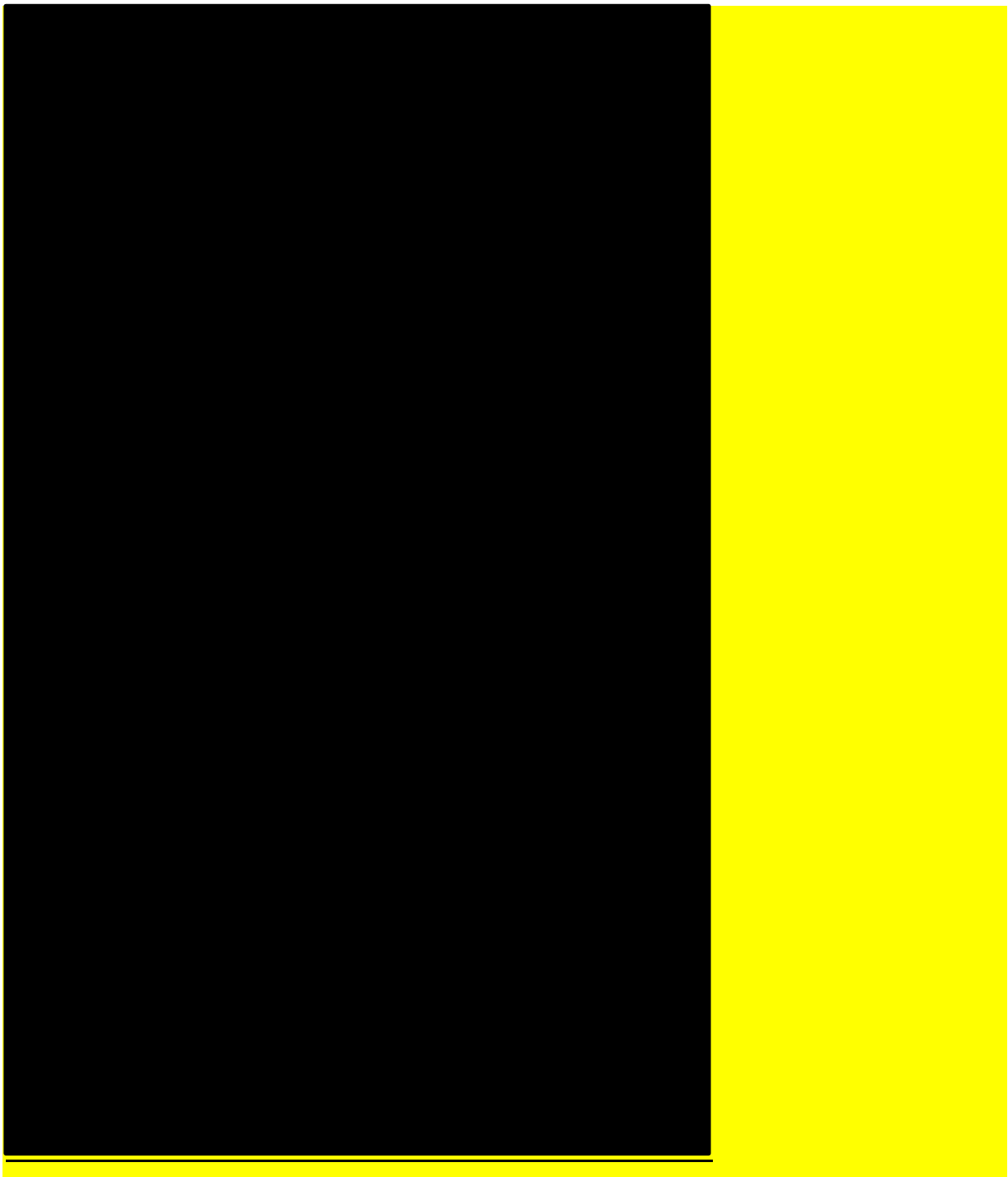
**Figure 4 KM curve of post-response survival in subjects who achieved complete of partial response (per IRRC by treatment arm - CheckMate 214 intermediate/poor risk (60 month minimum follow-up)**

**Figure 5 KM curve of time from randomization to first subsequent systemic anticancer therapy - CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up)**

**Figure 6 KM curve of time from randomization to second subsequent systemic anticancer therapy - CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up)**

**Figure 7 OS extrapolations for the Company base case (log-normal) and ERG preferred scenarios – CheckMate 214 intermediate/poor-risk patients (60-month minimum DBL)**

**Figure 8: OS smoothed hazard plots of CheckMate 214 data from the 48-month minimum DBL (black) and 60-month minimum DBL (blue) with all patients censored from the time point indicated in the figure**



Black solid line = 48-month minimum DBL; blue dashed line = 60 month minimum DBL. Circles highlight end of smoothed hazard plots and pattern of change between plots by adding an additional month of data for patients. A 12-month smoothing interval was used for hazard plots.

Figure 9. OS smoothed hazard plots of CheckMate 214 data and corresponding KM data from A) 30-month minimum DBL, B) 42-month minimum DBL, C) 48-month minimum DBL, D) 60-month minimum DBL.

Note: Circles highlight pattern of smoothed hazard curves in heavily censored portion of the KM curve, with arrows indicating sunitinib hazard and corresponding KM data and numbers of patients at risk. A 12-month smoothing interval was used for hazard plots.

**Figure 10. OS smoothed hazard plots of CheckMate 214 data across 30-month minimum DBL 42-month minimum DBL, 48-month minimum DBL, 60-month minimum DBL**

Note: Vertical dashed lines represent minimum follow-up for corresponding DBL. A 12-month smoothing interval was used for hazard plots.

**Figure 11. Estimated hazard ratio and 95% CI for CheckMate 214 OS over 180 months (15 years)**

# References

[1] Tannir NM, Motzer RJ, McDermott DF, et al. First-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in patients with long- term survival of ≥5 years in the CheckMate 214 trial. Presented at: IKCS 2021; November 5-6, 2021. Abstract CTR11.

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[3] Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. (Updated: March 2013) Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/pdf/PubMedHealth_PMH0089910.pdf. Accessed: 14 December 2017

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[5] Jackson C. Package 'flexsurv': Flexible Parametric Survival and Multi-State Models. https://cranr-projectorg/web/packages/flexsurv/flexsurvpdf. 2021;

[6] National Institute for Health and Care Excellence (NICE). TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma 2020. Available at: https://www.nice.org.uk/guidance/ta650. Accessed: 6 September 2021.

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[8] Kuusk T, Cullen D, Neves JB, Campain N, Barod R, Boleti E, El-Sheihk S, Grant L, Kelly J, Marchetti M, Mumtaz F, Patki P, Ramachandran N, Silva P, Tran-Dang MA, Walkden M, Tran MGB, Powles T, Bex A. Impact of the first surge of the COVID-19 pandemic on a tertiary referral centre for kidney cancer. BJU Int. 2021 May 8:10.1111/bju.15441. doi: 10.1111/bju.15441. Epub ahead of print. PMID: 33964109; PMCID: PMC8239749.

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# Clinical expert statement and technical engagement response form

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking for your details and your considerations of any potential equalities issues. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. The NICE technical team have also added some questions related to a potential key issue for your consideration. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 November 2021.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Clinical expert statement

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

NICE National Institute for Health and Care Excellence

# Part 1: About you and any potential equalities issues

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Dr Natalie Charnley |
| **2. Name of organisation** | RCR/RCP |
| **3. Job title or position** | Consultant Oncologist |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with metastatic renal cell carcinoma?<br>☐ A specialist in the clinical evidence base for metastatic renal cell carcinoma or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any** | None |

| | |
|---|---|
| **potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this appraisal could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

# Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

| | |
|---|---|
| **Ratio of intermediate- to poor-risk patients (ERG report section 1.2 [issue 2] and 4.3)**<br>There are fewer poor-risk patients in the CheckMate 214 trial (21%) than in the SACT dataset (35%). | |
| • What proportion of patients in clinical practice would be categorised as poor-risk, as defined by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (i.e. 3-6 prognostic factors)? | 20% in normally practice -depends on demographics of practice to some extent |
| • Would you expect COVID 19 to have had an impact on the proportion of people with poor risk being treated in clinical practice and captured in the Systemic Anti-Cancer Therapy (SACT) database? (for those with applications for treatment between 4 April 2019 and 30 November 2020) | May have increased numbers of patients presenting late, and hence more poor risk patients |
| **Subsequent treatments (ERG report section 3.4)** | |

Clinical expert statement

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| [redacted] of people in CheckMate-214 who received nivolumab with ipilimumab first-line proceeded onto subsequent treatments and 29% (234/814) from SACT proceeded onto second-line treatments. | |
| • Are the subsequent treatments reported in CheckMate 214 (table 11 of company submission and table 7 of ERG report) at 60 months/5 years representative of subsequent treatments used in current clinical practice, after both nivolumab with ipilimumab or sunitinib?<br>For example, the proportion of people treated with sunitinib and pazopanib, everolimus and lenvatinib (on their own or in combination) after nivo+ipi? And would nivolumab monotherapy be offered after nivo+ipi? | In current practice, more patients would have cabozantanib 2nd and 3rd Line.<br>At least 60% of patients would now have cabozantanib following both ipilimumab nivolumab or sutent<br>Less axitinib is now given, less than 10% following both ipilimumab nivolumab or sutent<br>Somewhat less sutent would be offered following both ipilimumab nivolumab , around 30%<br>Very little everolimus would be offered following both ipilimumab nivolumab or sutent<br>Less pazopanib would be offered following ipilimumab nivolumab, perhaps <10%. Tivozanib may also be offered in 10% of cases<br>Nivolumab wouldn't routinely be offered 2nd line after ipilimumab nivolumab |
| • Are the distribution of second-line treatments reported from SACT (see table 8 of ERG report, also reproduced below) at a minimum follow-up of 5 months representative of second-line treatments used in clinical practice? | Agree with the distribution<br>Dabrafenib+trametinib, Carboplatin+pemetrexed, Irinotecan+MdG+panitumumab not commonly used |
| • Would you expect the distribution of second-line treatments (i.e. the types and rates) to be different after around 5 months of treatment than after several years of treatment, for those who were treated with nivo+ipi or sunitinib? (i.e. would those who stopped their initial treatment early have | For patients who stop ipilimumab nivolumab early due to progression, would be more likely to use cabozantanib 2nd line |

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| different subsequent treatments than those who stopped their treatment after five years) | For patients who stop early due to toxicity or stop after several years, more likely to use sunitinib or tivozanib 2nd line |
| **Are there any important issues that have been missed in ERG report?** | No |

Thank you for your time.

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# Clinical expert statement and technical engagement response form

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing 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. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking for your details and your considerations of any potential equalities issues. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. The NICE technical team have also added some questions related to a potential key issue for your consideration. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 November 2021.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Clinical expert statement

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

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# Part 1: About you and any potential equalities issues

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Richard Griffiths |
| **2. Name of organisation** | Clatterbridge Cancer Centre |
| **3. Job title or position** | Consultant in Medical Oncology |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with metastatic renal cell carcinoma?<br>☐ A specialist in the clinical evidence base for metastatic renal cell carcinoma or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any** | None |

| | |
|---|---|
| **potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this appraisal could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

# Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

| | |
|---|---|
| **Ratio of intermediate- to poor-risk patients (ERG report section 1.2 [issue 2] and 4.3)**<br>There are fewer poor-risk patients in the CheckMate 214 trial (21%) than in the SACT dataset (35%). | |
| • What proportion of patients in clinical practice would be categorised as poor-risk, as defined by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (i.e. 3-6 prognostic factors)? | Approximately 30% |
| • Would you expect COVID 19 to have had an impact on the proportion of people with poor risk being treated in clinical practice and captured in the Systemic Anti-Cancer Therapy (SACT) database? (for those with applications for treatment between 4 April 2019 and 30 November 2020) | No |
| **Subsequent treatments (ERG report section 3.4)**<br>[redacted] of people in CheckMate-214 who received nivolumab with ipilimumab first-line proceeded onto subsequent treatments and 29% (234/814) from SACT proceeded onto second-line treatments. | |

Clinical expert statement

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|---|---|
| • Are the subsequent treatments reported in CheckMate 214 (table 11 of company submission and table 7 of ERG report) at 60 months/5 years representative of subsequent treatments used in current clinical practice, after both nivolumab with ipilimumab or sunitinib?<br>For example, the proportion of people treated with sunitinib and pazopanib, everolimus and lenvatinib (on their own or in combination) after nivo+ipi? And would nivolumab monotherapy be offered after nivo+ipi? | The standard treatment on progression following nivo/ipi would be a TKI monotherapy of which one can choose either sunitinib, pazopanib, cabozantinib or tivozanib. It is the opinion of this investigator that the choice of TKI likely makes very little difference to long term outcome. Choice of agent is driven by institutional familiarity, clinical experience and toxicity. The numbers shown are realistic but would now likely show a higher proportion of patients receiving the newer agents of tivozanib, cabozantinib and lenvatinib/everolimus. Nivolumab is not available for use in standard UK practice following progression on nivo/ipi and would not be regared as standard |
| • Are the distribution of second-line treatments reported from SACT (see table 8 of ERG report, also reproduced below) at a minimum follow-up of 5 months representative of second-line treatments used in clinical practice? | I think these are representative of routine clinical practice |
| • Would you expect the distribution of second-line treatments (i.e. the types and rates) to be different after around 5 months of treatment than after several years of treatment, for those who were treated with nivo+ipi or sunitinib? (i.e. would those who stopped their initial treatment early have different subsequent treatments than those who stopped their treatment after five years) | Not for nivo/ipi as would likely move onto a TKI monotherapy of which would select from those available. As discussed above the outcomes are going to similar irrespective of agent choice<br>It would be fifferent for sunitnib. Stopping at 5 months would almost certainly favour use of nivolumab in second line due to concerns about angiogenesis resistance whereas stopping at 5 years would likely mean offering another disease is intrinsically sensitive and would likely offer another TKI |
| **Are there any important issues that have been missed in ERG report?** | None |

Thank you for your time.

## Your privacy

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# Patient expert statement and technical engagement response form

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

In part 1 we are asking you about living with metastatic renal cell carcinoma or caring for a patient with metastatic renal cell carcinoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. The NICE technical team have also added some questions related to a potential key issue for your consideration.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

**You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.**

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

## Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **17 November 2021.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Living with this condition or caring for a patient with metastatic renal cell carcinoma

**Table 1 About you, metastatic renal cell carcinoma, current treatments and equality**

| | |
|---|---|
| **1. Your name** | |
| **2. Are you (please tick all that apply)** | ☐ A patient with metastatic renal cell carcinoma?<br>☐ A patient with experience of the treatment being evaluated?<br>☐ A carer of a patient with metastatic renal cell carcinoma?<br>☒ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | Kidney cancer UK |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☒ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☐ I am drawing from personal experience<br>☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Patient feedback<br>☐ I have not completed part 2 of the statement |

| | |
|---|---|
| **6. What is your experience of living with metastatic renal cell carcinoma?**<br>**If you are a carer (for someone with metastatic renal cell carcinoma) please share your experience of caring for them** | I work as a nurse for Kidney cancer UK, providing emotional support and education to patients and their families.<br>I regularly attend patient support groups and listen to their experiences and offer support and advice. I read daily posts from patients on the facebook support group pages and speak with patients on the charity careline. Living with kidney cancer can be very difficult for patients and the main concerns patients have voiced are fears of the cancer progressing, not having support after surgery, getting their scan results, the treatment failing, fears of surgery and coping with the side effects of medication. |
| **7a. What do you think of the current treatments and care available for metastatic renal cell carcinoma on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | I think the current treatments work well for some patients but not all, and it is reassuring for patients having more treatment options becoming available which have improved results. Everyone has such a different experience of their treatments, some can tolerate the medication well while others have to stop treatment early.<br>Many patients have reported that their treatment was very effective and some had scan results that showed no evidence of disease. Others didn't respond well and couldn't tolerate the side effects and some were hospitalised with severe colitis and pneumonia. |
| **8. If there are disadvantages for patients of current NHS treatments for metastatic renal cell carcinoma (for example, how sunitinib or pazopanib is given or taken, side effects of treatment, and any others) please describe these** | Living with the side effects of the treatment such as diarrhoea and fatigue are very challenging for some patients and this does interfere with their quality of life. Some patients reported that they do not have energy to socialise much or are embarrassed about their diarrhoea so won't go out to social gatherings. |
| **9a. If there are advantages of nivolumab with ipilimumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** | Some patients responded very well to Nivolumab and Ipilimumab and had good disease control with less side effects compared to current treatments. Some patients were able to continue working, maintain hobbies and travel on holiday with their families.<br>Patients and their families felt more positive knowing the treatment was working which gave them hope. |

| | |
|---|---|
| **9c. Does nivolumab with ipilimumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | In some patients, yes. One patient in particular reported minimal side effects and his latest scan result showed no evidence of disease. He was very pleased with the effectiveness of the treatment and felt more optimistic about his future. |
| **10. If there are disadvantages of nivolumab with ipilimumab over current treatments on the NHS please describe these.**<br>For example, are there any risks with nivolumab with ipilimumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why | Some patients have had serious side effects such as colitis and pneumonia which required hospitalisation and had to discontinue their treatment. |
| **11. Are there any groups of patients who might benefit more from nivolumab with ipilimumab or any who may benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | Patients who are not suitable for other treatments or who cannot take oral medication due to neurological problems or who have loss of hand dexterity may benefit from IV infusions. |
| **12. Are there any potential equality issues that should be taken into account when considering metastatic renal cell carcinoma and nivolumab with ipilimumab? Please explain if you think any groups of people with this condition are particularly disadvantaged**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics | None known |

| | |
|---|---|
| More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | |
| **13. Are there any other issues that you would like the committee to consider?** | No |

# Part 2: Technical engagement questions for patient experts

## Issues arising from technical engagement

The issues raised in the ERG report or by the NICE technical team are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

| **Ratio of intermediate- to poor-risk patients (ERG report section 1.2 [issue 2] and 4.3)**<br>There are fewer poor-risk patients in the CheckMate 214 trial (21%) than in the SACT dataset (35%). | |
|---|---|
| • What proportion of patients in clinical practice would be categorised as poor-risk, as defined by International | |

Patient expert statement

| | |
|---|---|
| Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (i.e. 3-6 prognostic factors)? | |
| • Would you expect COVID 19 to have had an impact on the proportion of people with poor risk being treated in clinical practice and captured in the Systemic Anti-Cancer Therapy (SACT) database? (for those with applications for treatment between 4 April 2019 and 30 November 2020) | |
| **Subsequent treatments (ERG report section 3.4)**<br>[redacted] of people in CheckMate-214 who received nivolumab with ipilimumab first-line proceeded onto subsequent treatments and 29% (234/814) from SACT proceeded onto second-line treatments. | |
| • Are the subsequent treatments reported in CheckMate 214 (table 11 of company submission and table 7 of ERG report) at 60 months/5 years representative of subsequent treatments used in current clinical practice, after both nivolumab with ipilimumab or sunitinib?<br>For example, the proportion of people treated with sunitinib and pazopanib, everolimus and lenvatinib (on their own or in combination) after nivo+ipi? And would nivolumab monotherapy be offered after nivo+ipi? | |
| • Are the distribution of second-line treatments reported from SACT (see table 8 of ERG report, also reproduced below) at a minimum follow-up of 5 months representative of second-line treatments used in clinical practice? | |
| • Would you expect the distribution of second-line treatments (i.e. the types and rates) to be different after around 5 months of treatment than after several years of treatment, for those who were treated with nivo+ipi or sunitinib? (i.e. would those who stopped their initial treatment early have different subsequent treatments than those who stopped their treatment after five years) | |

Patient expert statement

| | |
|---|---|
| **Are there any important issues that have been missed in ERG report?** | |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Having new treatments made available is very reassuring for patients.
- How people respond to their treatment is very individualised.
- Some patients have had excellent disease control on this treatment.
- The treatment has improved the quality of life in some patients.
- IV treatment could be more beneficial for some people.
-
-

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

# Technical engagement response form

## Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (CDF review of TA581) [ID3880]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

## Information on completing this form

We are asking for your views on key issues that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. The NICE technical team have also added a potential key issue.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **17 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

Technical engagement response form

# About you

**Table 1 About you**

| | |
|---|---|
| **Your name** | Sophia Ho |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Bristol Myers Squibb |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |

# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the ERG report or by the NICE technical team.

**Table 2 Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Company overall survival model projections for patients who received NIVO+IPI in the first-line setting do not reflect the CheckMate 214 trial 60-month minimum | Yes | BMS reinforce that the company base case is appropriate and supported by clinical data provided in the CDF exit company submission, clinical expert opinion, and additional data provided in this response. BMS reiterate that an equal hazard of death approach is clinically implausible and inappropriate for decision making as it is not based on sufficient clinical evidence, clinical expectation for those patients who are still alive at 5 years in both arms of CheckMate 214 (for whom the overall survival (OS) extrapolations are of relevance), or in line with prior precedent in similar appraisals in aRCC or solid tumour oncology by NICE. Further evidence is provided from CheckMate 214 supporting the long-term survival outcomes of those treated with NIVO+IPI versus sunitinib, in particular evidence for patients for whom the long-term survival extrapolations are most relevant (i.e. those with an OS of 5 years or more). Additional analyses have been performed to explore validity underpinning the ERGs equal hazard of death scenarios and the plausibility of the company long-term overall survival projections, and are provided herein. |

follow-up overall survival data

**Comparison of company base case compared with CheckMate 214 60-month minimum follow-up data**

BMS disagree with the interpretation that the company OS projections do not reflect the CheckMate 214 60-month follow-up data. Considering the economic model incorporates the area under the curve in calculations, Kaplan-Meier (KM) data were compared with the company base case over the minimum available follow-up. As shown in Table 1, restricted mean overall survival (OS) over 60 months is [redacted] months for NIVO+IPI and [redacted] months for sunitinib (difference between arms of [redacted] months or more than [redacted] years). When compared to the KM restricted means, the company model extrapolations result in a [redacted] of mean OS for NIVO+IPI and [redacted] of mean OS for sunitinib, both of which are [redacted] in magnitude versus the KM data. Therefore, BMS believe the company survival projections reflect the 60-month data accurately for both arms, and that the extrapolations appropriately reflect the observed OS events to 60 months.

**Table 1. Comparison of restricted mean OS (area under the curve) to 60 months between CheckMate 214 KM data and company base case extrapolations**

| | CheckMate 214 KM data (60-month minimum DBL) | | Company base case (independent log-normal) | |
|---|---|---|---|---|
| | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Restricted Mean Survival to 60 months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Difference versus KM data | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | | | [redacted] | [redacted] |

BMS believe that interpretation of long-term OS projections in the economic model cannot be separated from clinical interpretation of the patients who are, in fact, alive at 60 months, as survival of these patients is what the model predicts over the rest of the model time horizon. Therefore, the OS events just prior to 60 months should not be viewed as more relevant or having greater importance than the clinical status of intermediate/poor risk aRCC patients who are still alive at 5 years. BMS reinforce that patient status will have an influence on longer term survival (i.e. whether at 5 years a patient is progression-free and off therapy, progression-free and still on first-line therapy, still remaining in response, or progressed) and the number of line(s) of therapy received are also essential to inform the OS projections of these patients past 5 years.

**Conditional survival analyses - Patients with overall survival of at least 5 years**

As the 60-month minimum follow-up mark has now been reached, it is now the remaining patients who have survived up until this 5-year timepoint who are subject to extrapolation assumptions as their outcomes are still uncertain. In total, there are 163 NIVO+IPI patients and 113 sunitinib

| | | |
|---|---|---|
| | | patients with an OS of at least 5 years who are considered in this analysis, representing 38.4% and 26.5% of patients from the CheckMate 214 study, respectively.[1]<br>Similar to the 60-month minimum follow-up data previously presented (CS sections A.6.1.2, response to clarification question B1), NIVO+IPI patients with an OS of at least 5 years are continuing to benefit from their first-line treatment, as the median duration of response (DoR) still has not been met for NIVO+IPI compared with 23.5 months (95% CI: 18.2-60.4 months) with sunitinib (see Figure 1) and among responders who have an OS of 5 years or more, 75.0% of NIVO+IPI patients have a durable response of at least 60 months compared with 38.0% of patients in the sunitinib arm (see Table 3). The higher proportion of patients responding to treatment is also reflected in<br>Figure 2 where 71.3% of patients who are alive at 5 years had a tumour reduction greater than or equal to 50%, whereas in the sunitinib arm 37.0% of patients experience such a reduction.<br>**Consistent with the 60-month data cut presented in the company submission for intermediate-/poor-risk patients in CheckMate 214, patients with an OS of at least 5 years continue to demonstrate a substantial improvement in PFS compared with patients treated with sunitinib. The HR has improved from [redacted] with all patients regardless of OS, to HR [redacted], meaning patients in the NIVO+IPI arm who have an OS of 5 years or more have a 65% reduction in the risk of progression versus those who received sunitinib and are alive at 5 years. In patients alive at 5 years, the [redacted] with NIVO+IPI as [redacted] of patients remain progression-free, which is [redacted] of sunitinib patients ([redacted])of sunitinib patients and a median PFS of [redacted] months (HR [redacted]) (see Table 2 and [redacted]** |

Figure 3). More specifically, when considering the patients who experienced a response (either a complete response (CR) or a partial response (PR)) as their best overall response (representing 70.6% of NIVO+IPI patients versus 50.0% of sunitinib patients alive at 5 years), [redacted] and [redacted] of NIVO+IPI and sunitinib patients remain progression-free, respectively (see Table 2). This data demonstrates that patients who achieve an objective response with NIVO+IPI are more likely to achieve clinically relevant benefits in terms of PFS benefits sustained with longer follow-up than patients who achieve a response with sunitinib (see Table 4), which is in line with clinical expert expectations in relation to for NIVO+IPI where given the PFS plateau, the PFS curve would eventually meet the OS curve, as a proportion of patients are expected to not have disease progression before death.[2].

**Table 2 Best overall response per IRRC and progression events per IRRC (secondary definition) for patients with OS at least 5 years, intermediate/poor risk patients**

| | Number of subjects n (%) | | Number of progression events per IRRC (secondary definition) n (%) | |
|---|---|---|---|---|
| | NIVO+IPI (n = 425) | Sunitinib (n = 422) | NIVO+IPI (n = 425) | Sunitinib (n = 422) |
| Patients with OS at least 5 years | 163 | 112 | 163 | 112 |
| Complete response (CR) | 40 (24.5) | 7 (6.3) | [redacted] | [redacted] |
| Partial response (PR) | 75 (46.0) | 49 (43.8) | [redacted] | [redacted] |

| | | | | | |
|---|---|---|---|---|---|
| Stable disease / non-CR / non-PD | 40 (24.5) | 38 (33.9) | [redacted] | [redacted] |
| Progressive disease (PD) | 7 (4.3) | 14 (12.5) | [redacted] | [redacted] |
| Unable to determine (UTD) | 1 (0.6) | 3 (2.7) | [redacted] | [redacted] |
| Not reported | 0 | 1 (0.9) | [redacted] | [redacted] |

**Table 3 Proportion of patients with DoR over different timepoints, intermediate/poor risk patients with OS at least 5 years from CheckMate 214**

| | Duration of response of at least (95% CI) | |
|---|---|---|
| | NIVO+IPI (n = 163) | Sunitinib (n = 112) |
| 24 months | [redacted] | [redacted] |
| 30 months | [redacted] | [redacted] |
| 36 months | [redacted] | [redacted] |
| 42 months | [redacted] | [redacted] |
| 48 months | [redacted] | [redacted] |
| 60 months | [redacted] | [redacted] |

**Table 4 PFS rate per IRRC (secondary definition) over different timepoints, intermediate/poor risk patients with OS at least 5 years from CheckMate 214**

| | PFS rate (95% CI) | |
|---|---|---|
| Median PFS | NIVO+IPI (n = 163) | Sunitinib (n = 112) |
| 12 months | [redacted] | [redacted] |

| | | |
|---|---|---|
| 24 months | [redacted] | [redacted] |
| 36 months | [redacted] | [redacted] |
| 48 months | [redacted] | [redacted] |
| 60 months | [redacted] | [redacted] |

As per the original company submission (TA581) and CDF review submission, the same criteria of including systemic therapies received by 5% or more patients in either arm at any time during the trial was applied in the economic model. Amongst patients with OS of at least 5 years, subsequent treatments received in the NIVO+IPI arm were almost half of that in the NIVO+IPI arm (39.3% versus 75.0%). This is further supported by the swimmer plots presented in the company submission (figure 53 and figure 54 of the CDF review company submission) demonstrating that amongst patients with an objective response (PR or CR) as their best overall response, [redacted] of NIVO+IPI patients are off treatment and have never received subsequent therapy versus [redacted] of patients in the sunitinib arm. These observations are in line with clinical expectations who expect a greater proportion of NIVO+IPI patients to not receive subsequent treatment because they do not need to, as they are still receiving clinical benefit from the long-term effects of NIVO+IPI, referencing the tail of the PFS curve where patients do not need any more treatment.[2]

**Evidence from CheckMate 214 60-month minimum follow-up**

| | | |
|---|---|---|
| | | BMS have previously provided a number of clinical outcomes in the company submission and response to clarification questions, for brevity they are not included here and BMS request that these continue to be considered in relation to the OS extrapolations.<br>NIVO+IPI patients who achieve a response (CR or PR) have improved post-response survival compared with sunitinib (HR [redacted]), with [redacted] that is [redacted] the follow-up period (see<br>Figure 4). This data demonstrates that NIVO+IPI patients who respond have improved OS over sunitinib patients. The improved post-response survival with NIVO+IPI is also in line with clinical expert expectations where patients who experience a durable response would be expected to achieve long-term survivorship, and that nivolumab monotherapy would be less effective at providing this long-term response than NIVO+IPI.[2] Considering that the proportion of patients still alive at 5 years and achieve response (as demonstrated above) is higher for NIVO+IPI, it would be clinically inappropriate to assume the risk of death would be equal to that of sunitinib.<br><br>The restricted mean survival time (RMST) for PFS per IRRC by secondary definition, time from randomization to first subsequent systemic anticancer therapy, second systemic anticancer therapy and OS is presented in Table 5. With increasing time, the benefits, as demonstrated by area under the KM curves, of the aforementioned endpoints increase between NIVO+IPI and sunitinib. Moreover, with a minimum follow-up of 60-months in CheckMate 214, NIVO+IPI has demonstrated an extension of [redacted] mean months to progression, [redacted] mean months to first subsequent treatment, |

[redacted] mean months to second subsequent treatment and [redacted] mean months extension to OS compared with the sunitinib.

**Table 5 Restricted mean survival time, intermediate/poor risk patients (minimum 60-month follow-up)**

| | NIVO+IPI (n = 425) | Sunitinib (n=422) | Difference (95%CI) | Ratio, NIVO+IPI versus Sunitinib (95% CI) |
|---|---|---|---|---|
| | PFS per IRRC, secondary definition | | | |
| 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | Time from Randomization to First Subsequent Systemic Anticancer Therapy | | | |
| 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | Time from Randomization to Second Subsequent Systemic Anticancer Therapy | | | |
| 12-months | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | OS | | | |
| | | 12-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 24-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 36-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 48-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 60-months | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | Key: CI, confidence interval; RMST, restricted mean survival time. | | | |
| | | If the ERG's position that the survival benefit of NIVO+IPI diminishes from approximately 54 months were to be supported by the data from CheckMate 214, this would be reflected in a diminishing treatment effect after RECIST progression when patients go on to receive further subsequent lines of therapy. This can be captured by evaluating time from randomisation to second objective disease progression (PFS2), which can show whether randomised therapy has a negative effect on the efficacy of second-line treatment received after disease progression. The CheckMate 214 study did not include PFS2 as a secondary endpoint because RECIST data were not collected for subsequent therapies. However, it was possible to evaluate the exploratory endpoint of time from | | | | |

| | | |
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| | | randomisation to second subsequent therapy or death (TSST) as a proxy for PFS2, recognizing that some patients may discontinue treatment before initiating a further line of therapy. We also evaluated time from randomisation to first subsequent therapy (TFST) which is often considered to be a proxy for symptomatic disease progression on randomised therapy in cancer RCTs.<br>The KM plots of TFST and TSST from the CheckMate 214 60-month minimum follow-up are presented in<br><br>Figure 5 and<br><br>Figure 6 and a summary of the median and HR estimates (with 95% CIs) are provided in Table 6. It is apparent in the plot of TSST that treatment benefit with NIVO+IPI is [redacted], [redacted] on the efficacy of subsequent therapy, which further highlights the durability of treatment benefit, with a HR of [redacted] and a gain in median TSST of [redacted] months versus sunitinib (median TSST: [redacted] versus [redacted]. This is despite a significant proportion of sunitinib patients ([redacted]) being treated with nivolumab as a subsequent therapy post-progression. Similarly, NIVO+IPI patients experienced [redacted]TFST, with a HR of [redacted]) and a gain in median TFST of [redacted] months versus sunitinib (median TFST: [redacted] versus [redacted], respectively). It is also worth noting that, considering a proportion of patients still alive in the NIVO+IPI arm are still on first-line therapy when patients in the sunitinib arm are receiving |

subsequent nivolumab, the progression of disease is also of relevance in influencing OS. BMS reiterate that patients who have progressed on 1L sunitinib and receive nivolumab as 2L or 3L monotherapy experience worsening of their disease; therefore, any direct comparison of longer term survival of patients who have progressed and receive subsequent therapy with a first-line patient who is either in response or stable disease would be inappropriate.

**Table 6 Summary statistics for TFST and TSST by treatment – CheckMate 214 intermediate/poor risks patients (60-month minimum follow-up)**

| Endpoint | Treatment | N | Events | Censors | Median (m; 95% CI) | HR (95% CI) |
|---|---|---|---|---|---|---|
| TFST | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |
| | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |
| TSST | NIVO+IPI | 425 | [redacted] | [redacted] | [redacted] | [redacted] |
| | Sunitinib | 422 | [redacted] | [redacted] | [redacted] | [redacted] |

Key: TFST, time to first subsequent systematic anti-cancer therapy; TSST, time to second subsequent systematic anti-cancer therapy; CI, confidence interval, HR, hazard ratio; m, month; n, number.

**Table 7 Subsequent treatment split by treatment arm from CheckMate 214 intermediate/poor risk patients with OS of at least 5 years**

| | NIVO+IPI (n = 163) | | Sunitinib (n = 112) | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients who received systemic subsequent treatment | 64 | 39.3 | 84 | 75.0 |
| Nivolumab | 17 | 10.4 | 59 | 52.7 |
| Axitinib | 22 | 13.5 | 28 | 25.0 |
| Cabozantinib | 27 | 16.6 | 26 | 23.2 |
| Everolimus | [redacted] | [redacted] | [redacted] | [redacted] |
| Pazopanib | 19 | 11.7 | 6 | 5.4 |
| Sunitinib | 24 | 14.7 | 15 | 13.4 |
| Investigational antineoplastic | [redacted] | [redacted] | [redacted] | [redacted] |

**Mortality rates using alternative time intervals.**

The ERG have based their equal hazard of death assumption on annual mortality rates from CheckMate 214, including OS rates for when less than 5 patients are at risk in either arm (i.e. 6 years or 72 months). BMS challenge the appropriateness of this approach in using what seems to be an arbitrary time point versus leveraging individual patient level data and event times, as this annual OS rate method is not established in NICE DSU guidance documents for survival extrapolation.[3] In addition, when looking at the mortality rate over differing intervals other than the 12-month interval chosen by the ERG, the trend of the mortality rate is [redacted] NIVO+IPI versus sunitinib, [redacted] instances where the death rate is [redacted] for sunitinib; however, this trend is not consistent across intervals chosen for examination. As can be

seen in Table 8 and Table 9, the selection of time interval when assessing the mortality rate impacts the ability to derive conclusions on the hazard between the rates of NIVO+IPI and sunitinib. BMS reiterate that this is an inappropriate method of justification, subject to bias and should not be used to justify the use of an equal hazard between NIVO+IPI and sunitinib in absence of consideration of the clinical status of patients still alive at 5 years in both treatment arms. It should also be noted that amongst the patients who have OS of at least 5 years who are subject to the ERG's equal hazard of death assumption, [redacted] of NIVO+IPI patients are still progression-free compared with [redacted] in the sunitinib arm. Acceptance of an equal hazard of death assumption from 4.5 years would be analogous to accepting an assumption that patients who are on first-line therapy and those who are still responding (and may be free of disease, noting the proportion of patients alive at CR who have achieved and are still in CR), have the same risk of death as a patient who may be on his or her second-, third-, fourth- or later line of therapy. BMS reinforce that annual OS rates are not an established methodology and should not be considered justification or validation of an equal hazard of death assumption and that only clinically plausible assumptions should be considered appropriate for decision making, in line with the current draft proposed NICE new methods guidance.[4]

**Table 8 CheckMate 214 mortality rates over alternative time intervals - intermediate/poor risk (3, 6, 9 and 18 months)**

| | 3 months | 6 months | 9 months | 18 months |
|---|---|---|---|---|

| | | | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib | NIVO+IPI | Sunitinib |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 to 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 3 to 6 | [redacted] | [redacted] | | | | | | |
| | | 6 to 9 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 9 to 12 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| | | 12 to 15 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 15 to 18 | [redacted] | [redacted] | | | | | | |
| | | 18 to 21 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 21 to 24 | [redacted] | [redacted] | | | | | | |
| | | 24 to 27 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 27 to 30 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| | | 30 to 33 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 33 to 36 | [redacted] | [redacted] | | | | | | |
| | | 36 to 39 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 39 to 42 | [redacted] | [redacted] | | | | | | |
| | | 42 to 45 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 45 to 48 | [redacted] | [redacted] | | | [redacted] | [redacted] | | |
| | | 48 to 51 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| | | 51 to 54 | [redacted] | [redacted] | | | | | | |

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|---|---|---|---|---|---|---|---|---|
| 54 to 57 | [redacted] | [redacted] | [redacted] | [redacted] | | | | |
| 57 to 60 | [redacted] | [redacted] | | | | | | |

* - Asterix to denote occasions where the mortality rate is greater for NIVO+IPI than sunitinib

**Table 9 CheckMate 214 mortality rates over alternative time intervals - intermediate/poor risk (24 months)**

| | NIVO+IPI | Sunitinib |
|---|---|---|
| **0 to 24** | [redacted] | [redacted] |
| **12 to 36** | [redacted] | [redacted] |
| **24 to 48** | [redacted] | [redacted] |
| **36 to 60** | [redacted] | [redacted] |

**The ERG's preferred modelling of overall survival does not adequately reflect the CheckMate 214 60-month minimum follow-up OS data**

The company notes that the ERG did not provide a visual assessment of the modelled OS from their preferred scenarios, which applied equal mortality hazards for the treatment arms from 54 months onwards. When implementing this in the company model, it was clear that the ERG's scenario leads to significant changes in long-term extrapolations, especially to the NIVO+IPI arm as a result of the assumption of equal mortality hazards with sunitinib being applied from 54 months (see

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| | | Figure 7). The company maintain that the base case OS modelling based on the log-normal distribution adequately reflects the observed trial data to the minimum 60-month follow-up and the long-term projections past 5 years may in fact be conservative for NIVO+IPI, considering the clinical data presented and clinical status of patients alive in both arms at 5 years. This is further reflected in a comparison of RMST to 60-months follow-up from the CheckMate 214 trial and the company's base case model as presented in Table 1.<br><br>**Plausibility of company long-term overall survival projections**<br>When selecting appropriate extrapolations, investigation of visual fit to smoothed hazards is considered in addition to statistical fit criteria and clinical plausibility. In the case of CheckMate 214, an artificial upward trend is observed in the smoothed hazard plots for NIVO+IPI in the 60-month DBL starting at an earlier time point that contrasts with prior data cuts. Therefore, we have investigated this further to determine whether this was in fact a true difference in hazard pattern that should be considered or was an artefact of the methodology and unlikely to be truly reflective of the hazards for NIVO+IPI. As shown in the company response to clarification questions (Figure 2, left panel), with both database locks plotted to only 48 months of follow-up, the 60-month minimum DBL smoothed hazard plots [redacted] with the 48-month minimum DBL hazard data, with [redacted] for either treatment arm between DBLs. However, when plotting the 60-month minimum DBL to 60 months (Figure 2, right panel, in company response to clarification questions), the smoothed hazard [redacted] of the 48-month minimum DBL for both treatment arms |

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| | | (NIVO+IPI and SUN) from before 40 months. This [redacted] from the 48-month minimum DBL smoothed hazards demonstrates that information from later in the curve (past the point of minimum follow-up in the prior DBL), and the smoothing hazard function, have an impact on the appearance of the smoothed hazard, [redacted] (i.e., data earlier than the minimum follow-up from the previous DBL). Therefore, it is important to investigate [redacted] to clarify whether this [redacted].<br>The ERG have stated in their report (section 4.1, p. 26), "*However, as a minimum of 60 months follow-up data are available from the CheckMate 214 trial, there is no censoring before Month 60 and so the unsmoothed hazard rates between Month 48 and Month 60 are completely unaffected by censoring.*" BMS disagree that the unsmoothed hazards are unaffected to the point of minimum follow-up, and have provided plots of the unsmoothed hazards in Figure 3 of the company response to clarification questions. This figure clearly shows that the unsmoothed hazards at the bottom of the figure for the 60-month minimum DBL (blue dashed line) [redacted] the unsmoothed hazard from the 48-month minimum DBL (yellow dashed line) up to the point of minimum follow-up for the 48-month DBL. After this point of 48 months, after which many patients are censored in both treatment arms, the yellow spikes of unsmoothed hazards from the 48-month minimum DBL can be [redacted] from the blue unsmoothed hazards from the 60-month minimum DBL for both NIVO+IPI (left panel) and SUN (right panel). In addition, where the yellow spikes are observed for |

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| | | both panels, it is clear the blue hazard is not experiencing high spikes for either treatment arm after 48 months until after 60 months (i.e. the minimum follow-up from the 60-month DBL).<br>In contrast, **smoothed hazards** can be affected by censoring and differing lengths of included follow-up, as shown in Figure 2 in the company response to clarification questions, and demonstrated below in<br><br>Figure 8, Figure 9 and Figure 10. To further demonstrate the impact and influence of 1 month of additional included follow-up on the smoothed hazard plot, additional plots were produced whereby all patients in the 48- and 60-month minimum DBLs were censored at a specific time point, which was varied by 1 month from 48 months to 60 months of follow-up (<br><br>Figure 8). As highlighted by the circles in each panel within the figure, the tails of the hazards vary for both DBLs with just one additional month of data for both treatment arms. The ERG believes that the hazard should be set as equal between treatment arms from 54 months; however, the smoothed hazards for data censored from [redacted] months do not support this assumption in<br><br>Figure 8. As described above, a change in pattern in the 60-month smoothed hazard plot is observed where both arms [redacted] from the 48-month minimum follow-up at an earlier time point than the minimum follow-up (i.e. 40 months or earlier), which demonstrates that this deviation and pattern is an artefact and should not be used for decision making as this may be resolved with |

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| | | longer trial follow-up, as demonstrated in Figure 9, and Figure 10 below. Figure 9 presents the OS smoothed hazard plots (12-month smoothing interval) along with the corresponding OS KM data published for CheckMate 214 across the DBLs, namely the 30-month minimum, 42-month minimum, 48-month minimum, and 60-month minimum DBLs, while Figure 10 presents these smoothed hazards for the four DBLs overlaid in a single plot.<br><br>**Equal hazard of death plausibility over the long-term**<br>To further investigate the plausibility of the ERG's position that mortality hazards for patients in the NIVO+IPI and sunitinib arms should be set equal from 54 months onwards, an additional analysis was performed to understand at what point parametric hazards cross, which would correspond to an equal hazard of death time point over a 15-year horizon.<br><br>First, the parameter estimates and the variance-covariance matrix were used to generate 50,000 bootstrapped log hazard rate samples over the 15-year horizon for both NIVO+IPI and sunitinib. Second, the OS time-varying HRs for NIVO+IPI versus sunitinib were estimated by calculating the exponentiated difference in the log hazard rates between the bootstrapped log hazard rate samples. As a result, the median, 2.5%, and 97.5% quantile hazard ratio estimates over time are plotted in<br><br>Figure 11. All analyses were conducted in R using the flexsurv package[5]. |

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| | | As shown in<br><br>Figure 11 in this figure that the median HR of the two models [redacted] and [redacted]. Further, while the 95% CI of the hazard ratio is initially very wide, it gets narrower around [redacted] and from month [redacted]. The percentage of simulations (i.e. the probability) during the 180 month horizon that resulted in an OS HR > 1 for NIVO+IPI versus sunitinib were calculated. Overall, these analyses showed that at 54 months, the percentage of simulations where the HR of NIVO+IPI vs. sunitinib was ≥1 was [redacted]. Furthermore, between [redacted] months, the percentage of simulations with a HR ≥1 reached a maximum of [redacted], indicating an [redacted] of equal hazards between NIVO+IPI and sunitinib over 15-years, based on the available follow-up in CheckMate 214.<br><br>**Precedent from previous NICE appraisal of IO therapies in aRCC**<br>Further to this, BMS would argue that, if the Committee were to agree with the ERG's suggestion of equalising the model mortality hazards for patients in the NIVO+IPI and sunitinib arms from 54 months onwards, this would be inconsistent with previous Committee positions on IO based therapies in aRCC in terms of durability of treatment effect and its relationship with a maximum treatment duration in the trial (treatment stopping rule). The CheckMate 214 trial and the marketing authorisation for NIVO+IPI in untreated intermediate/poor risk aRCC does not apply stopping rules |

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| | | for nivolumab and consequently the Committee concluded that no stopping rules should be applied in the cost-effectiveness model.<br><br>For example, in the appraisal of pembrolizumab plus axitinib for untreated aRCC, which is based on a 2-year stopping rule applied to the pembrolizumab arm in the KEYNOTE-426 study, the committee noted that in previous NICE appraisals of checkpoint inhibitors when length of treatment was capped at 2 years in the cost-effectiveness model, the committee did not assume lifetime treatment benefit but examined various analyses of treatment benefit waning effects.). The committee agreed that there would likely be a durable response from immunotherapy but concluded that there was insufficient evidence to assume this would be lifelong. The committee considered model scenarios when the treatment effect of pembrolizumab stopped after 3 years, 5 years and 10 years (that is, treatment effect continued to 1 year, 3 years and 8 years after stopping pembrolizumab). Although the committee concluded that the immaturity of the data from KEYNOTE-426 (approximately 20 months follow-up) made any estimation of treatment waning effect highly uncertain, it accepted scenarios when a waning effect was applied after 5 years [TA 650 FAD sections 3.10-3.11]. [6]<br><br>Conversely, in the appraisal of avelumab plus axitinib for untreated aRCC, based on clinical evidence from the JAVELIN Renal 101 trial, which has no maximum treatment duration, the committee concluded that there was no clinical evidence to support a stopping rule and that it |

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| | | should not be in the model. The committee concluded that there was no evidence to support what proportion of patients would have a long-term treatment effect after stopping treatment. Therefore, the modelling should have accounted for a range of potential options, including the potential for no patients to have a long-term treatment effect after stopping treatment. The committee was aware that the company's final model had removed the stopping rule, so the model also excluded treatment waning (that is, because treatment now continued in the model, as aligned with the trial, there was no need to apply assumptions around what happens to the treatment effect after stopping treatment at a set time period, rather than for adverse events or progression). The committee agreed that this approach was appropriate. [TA645 FAD Sections 3.16-3.17].[7]<br><br>It is worth noting that approaches in other solid tumor TAs have also considered a lasting effect of nivolumab after cessation, based on long-term evidence, whereby the committee agreed that the effect, while uncertain, likely lasted "at least three years". In addition, in [redacted].<br><br>Based on the latest 60-month DBL, [redacted] patients in the NIVO+IPI arm were still receiving nivolumab treatment at 54 months and the model (based on the best-fitting [redacted]) further projected that nearly all patients (i.e. just above 99%) in the NIVO+IPI arm would complete their treatment by approximately [redacted] years follow-up. In contrast, approximately [redacted] of patients in the |

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| | | sunitinib arm were still on randomised treatment at 54 months. In addition, approximately [redacted] of patients were still progression-free in the NIVO+IPI arm versus [redacted] in the SUN arm. The company would therefore consider it would be inappropriate to assume equal mortality hazards for N+I versus sunitinib after 54 months [redacted] BMS consider that any assuming impact on mortality hazards between NIVO+IPI and sunitinib prior to all patients completing treatment (with nivolumab) is in contrast with prior solid tumour assessments of immunological therapies, where treatment waning has been considered and/or included in the final base case. |
| **ERG response** | | **Comparison of company base case compared with CheckMate 214 60-month minimum follow-up data**<br>The company model accurately predicts CheckMate 214 median OS results. However, this is not evidence that the model accurately predicts OS beyond the point in time that median OS is reached.<br><br>**Conditional survival analyses - patients with overall survival of at least 5 years**<br>The evidence presented in Table 7 shows that, in the CheckMate 214 trial:<br>• of the 163 patients still alive at 5 years in the NIV+IPI arm, 64/163 (39.3%) had received subsequent treatment and, of these, 17/64 (26.5%) had received nivolumab |

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| | | • of the 112 patients still alive at 5 years in the sunitinib arm, 84/112 (75.0%) had received subsequent treatment and, of these 59/84 (70.2%) had received nivolumab<br>• of those in the sunitinib arm alive at 5 years, 77.6% had either received no subsequent treatment or had received nivolumab as a subsequent therapy.<br>The ERG considers that the reasons for the convergence in the mortality hazards seen in the two arms of the CheckMate 214 trial between years 4 and 5 are:<br>• there is a high percentage of patients in the sunitinib arm who were still alive at 5 years who had received nivolumab second-line<br>• approximately 25% of patients in the sunitinib arm who were still alive at 5 years had had a sustained response to sunitinib.<br>The ERG does not consider the convergence is '*analogous to accepting an assumption that patients who are on first-line therapy and those who are still responding (and may be free of disease, noting the proportion of patients alive at CR who have achieved and are still in CR), have the same risk of death as a patient who may be on his or her second-, third-, fourth- or later line of therapy*'. Even if it were analogous, the data from the CheckMate 214 trial support convergence being the case.<br><br>The TSST analysis undertaken by the company does not provide evidence about the outcomes for the CheckMate 214 60-month survivors as it is an analysis of data from all patients in the trial. |

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| | | **The ERG's preferred modelling of overall survival does not adequately reflect the CheckMate 214 60-month minimum follow-up OS data**<br>The ERG's preferred modelling of OS mirrors the company model up to month 54 and is in line with the 60-month follow-up data from the CheckMate 214 trial.<br>**Equal hazard of death plausibility over the long term**<br>The company has provided insufficient evidence to allow the ERG to fully critique the company approach. Nevertheless, the ERG considers that, within the CheckMate 214 trial, mortality hazards crossed in year 5 and, therefore, the advantage of a bootstrapped analysis in this appraisal is unclear.<br><br>**Precedent from previous NICE appraisal of IO therapies in aRCC**<br>The company appears to be conflating treatment waning with an equalisation of mortality hazards over time. Although treatment waning would cause a convergence of mortality hazards between two treatments, the ERG does not consider that this is the likely cause of the equalisation of mortality hazards seen between the two arms of the CheckMate 214 trial.<br><br>**Mortality rates using alternative time intervals**<br>Table 8 presented by the company supports the ERG's position as, from month 48, the CheckMate 214 trial data show that 6-month mortality rates were slightly higher for patients in the NIV+IPI arm |

than in the sunitinib arm. The ERG's assumption that mortality hazards for the NIV+IPI and sunitinib arms equalise from month 54 onwards may, therefore, be conservative.

**Plausibility of company long-term overall survival projections**

The hazard rates considered by the ERG were taken directly from the CheckMate 214 trial and were presented in our original report (reproduced in Table A):

Table A CheckMate 214 trial annual mortality rates (Table 10 in the ERG report)

| Year | NIVO+IPI | Sunitinib |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |
| 6* | [redacted] | [redacted] |

* CheckMate 214 trial data provided in the company model

Source: ERG calculated rates using data from CDF Review CS, Table 5

The annual mortality rates during the first 5 years are unaffected by censoring or smoothing and provide evidence that mortality rates had converged between the two trial arms by year 5. The ERG

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| | | considers that results from the analysis of smoothed hazards presented by the company does not outweigh the direct evidence from the trial.<br><br>In summary, the ERG considers that the evidence presented in the company response to technical engagement either:<br>• supports mortality hazards for the NIV+IPI and sunitinib arms of the CheckMate 214 trial converging<br>• is not relevant to an assessment of whether mortality hazards converge or<br>• is speculative. |
| Fewer poor-risk patients in the CheckMate 214 trial than in the SACT dataset (21% vs 35%, respectively) | Yes | BMS would like to reiterate that the difference in proportions of intermediate and poor risk patients in CheckMate 214 was resolved in in the original appraisal (TA581) and that "The committee concluded that the combined intermediate- or poor risk group is appropriate for decision making.".<br><br>The ERG stated in their report that a difference in ratio of intermediate and poor risk patients "*only matters if there are differential outcomes and costs for these two groups of patients*". The CheckMate 214 study was not powered for analyses by subpopulations. However, a formal interaction test was conducted for OS and on PFS as assessed by IRRC (secondary definition) on the February 2021 (60-month minimum) data cut to further explore potential treatment |

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| | | heterogeneity in the pre-specified subgroups. From this interaction test, a p-value of <0.05 would indicate statistically significant “proof of different effects”.<br><br>For the purposes of displaying baseline characteristics, subgroups are retrieved from the Case Report Form (CRF) as this reflects the true patient population. For stratified analyses, stratification factors are based on data from IRT (Interactive Response Technology) collected at the time of the randomization. Therefore, the HR presented in the tables below for ‘overall’ (i.e. unstratified but intermediate/poor risk combined) differs from that presented in stratified analyses.<br><br>**IMDC risk score**<br><br>On the February 2021 (60-month minimum) data cut, an unstratified cox proportional hazard model was used to assess the significance of the interaction between the treatments and the subgroup based on IMDC intermediate risk score (1-2) or IMDC poor risk score (3-6) (excluding any patient with favourable risk). The unstratified cox proportional hazard model is based on treatment + IMDC + treatment*IMDC. In Table 10, the p-value for the test of interaction is [redacted]; HR are similar and favouring the N+I treatment arm in both subgroups with [redacted] of a quantitative or qualitative interaction between the treatment effect and the baseline IMDC prognostic score (i.e. poor and intermediate subjects) for OS. |

**Table 10 Subgroup analyses of overall survival from the CheckMate 214 study – IMDC risk score (minimum follow-up: 60 months)**

[redacted]

CheckMate 214 February 2021 (60-months minimum) DBL, CI=confidence interval; CRF=case report form; HR = hazard ratio; KME=Kaplan-Meier estimate; N.A.=not available.
(1) KME of median time to event.
(2) Unstratified Cox proportional hazard model. HR is NIVO+IPI over Sunitinib
(3) Unstratified Log-rank Test
(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup

Similar exploratory analysis of PFS (per IRRC, secondary definition) also showed consistent benefit for nivolumab + ipilimumab over sunitinib in the baseline IMDC prognostic score (i.e. poor and intermediate subjects) subgroups with [redacted] of a qualitative or quantitative interaction in this subgroup (p-value for interaction = [redacted];Table 11).

**Table 11 Subgroup analyses of progression-free survival (per IRRC, secondary definition) from the CheckMate 214 study – IMDC risk score (minimum follow-up: 60 months)**

[redacted]

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| | | CheckMate 214 February 2021 (60-months minimum) DBL, CI=confidence interval; CRF=case report form; HR = hazard ratio; KME=Kaplan-Meier estimate; N.A.=not available.<br>(1) KME of median time to event.<br>(2) Unstratified Cox proportional hazard model. HR is NIVO+IPI over Sunitinib<br>(3) Unstratified Log-rank Test<br>(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup<br><br>In intermediate/poor-risk subjects, OS favoured the NIVO+IPI group vs. the sunitinib group in all pre-defined subgroups. The IMDC risk subgroup analyses based on February 2021 DBL presented here confirmed that finding. There was [redacted] for qualitative or quantitative interactions between treatment and IMDC status (intermediate/poor). The exploratory analyses show that OS was significantly favoured in the NIVO+IPI group compared to the sunitinib group, regardless of IMDC risk score, as demonstrated by the difference in median time to event between arms and HRs.<br><br>Given that there is [redacted] of quantitative or qualitative interaction for either subgroup for OS and for PFS per IRRC (secondary definition) as described above, the results from CheckMate 214 for the combined intermediate-/poor-risk patient population are appropriate for assessment within this submission. The lack of proof of indication of different effects, combined with the fact the study was not powered to test outcomes for each risk group separately, demonstrates that the combined population is appropriate. |

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| | | **COVID-19 and the impact on SACT**<br>The collection of SACT data could have been impacted by the COVID-19 pandemic, as seen in the retrospective analysis of one of the largest referral centres in the UK; the Specialist Centre for Kidney Cancer at the Royal Free London NHS Foundation Trust.[8] This study demonstrated that during the first surge of the COVID-19 pandemic, diagnosis, referral and treatment of kidney cancer were severely impacted, seeing 2-week wait referrals decreasing by 50%, and the total number of patients discussed at specialist MDT meetings decreasing by 47%, despite the metastatic specialist MDT meetings remaining stable.[8]<br><br>In addition, an online survey of 41 clinical experts with experience treating metastatic clear cell RCC were questioned on treatment decisions outside and during the COVID-19 pandemic and the modifications of systemic therapy implemented.[9] Of the respondents, 71% of responded were clinical experts based in Europe. The majority of clinicians agreed that the IMDC risk score combined with a patients' fitness were considered relevant for factors for decision making. When comparing treatment options amongst fit, intermediate-/poor risk patient, the survey found that over 80% of clinicians would prescribe NIVO+IPI outside of the pandemic, however the pandemic resulted in a statistically significant decrease in the proportion of clinicians who would prescribe NIVO+IPI to 41%, with a third of clinicians preferring to prescribe a TKI. For those patients who are both unfit with an intermediate-/poor- risk, there was no significant change in treatment recommendations before or during the pandemic. The results of the online survey demonstrates |

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| | | that treatment modifications amongst fit, intermediate-/poor risk patients away from NIVO+IPI to a TKI during the pandemic would result in a greater proportion of unfit, intermediate-/poor risk patients being treated with NIVO+IPI.<br><br>Therefore, based on the above, BMS reiterate that the SACT data are not likely to be appropriate for determining the ratio of intermediate/poor risk patients treated in the NHS. In addition to limitations of the SACT data, which has less than 6 months of minimum follow-up, and the time of collection (during the COVID-19 pandemic), the lack of proof of difference of effects between the subgroups reinforces the conclusions of the committee in the original CS that the combined intermediate/poor risk population from CheckMate 214 is appropriate for evaluation of the cost-effectiveness of NIVO+IPI versus sunitinib in this assessment. |
| ERG comment | | The ERG considers that, if the split of intermediate-/poor risk patients in the CheckMate 214 trial does not match the split of intermediate/poor-risk patients treated in NHS practice, it is not necessarily the difference in effectiveness of NIV+IPI versus sunitinib by risk group that is a potential cause for concern. Rather, it is the absolute difference in outcomes between intermediate and poor-risk patients that is important as absolute differences in outcomes would mean that even if relative treatment effectiveness was the same regardless of risk group, the absolute effectiveness would be different. This means that the QALYs and costs for NHS patients treated with NIV+IPI in the NHS would be different to those estimated by the company model, and the ICER per QALY gained for the |

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| | | comparison of NIV+IPI versus sunitinib generated by the company model would not be generalisable to the NHS.<br><br>The ERG considers that the prescribing evidence provided by the company for patients with metastatic RCC is interesting, especially the evidence generated by the survey of European oncologists, and that this evidence supports the company's position that the use of TKIs was higher during the COVID-19 pandemic than it had been prior to the pandemic. However, the provided information is insufficient to conclude that the use of TKIs was higher in the UK during the period of data collection. |
| Subsequent therapy use varies between CheckMate-214 and SACT | No | BMS has no objection with the ERG position that subsequent treatments from CheckMate 214 is the most appropriate source of information. |

**Figure 1 KM curve of DOR, per IRRC - CheckMate 214 intermediate/poor risk patients with OS of at least 5 years with confirmed objective response[1]**

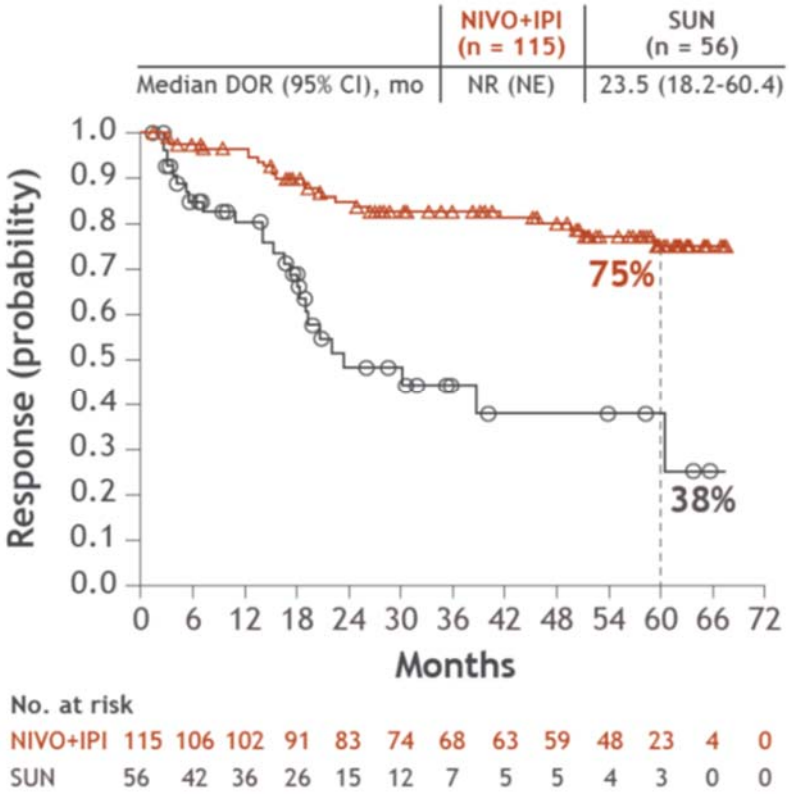

**Figure 2 Waterfall plot of best % reduction from baseline in sum of diameter of target lesions, IRRC - CheckMate 214 intermediate/poor risk patients with OS of at least 5 years**

**Figure 3 KM curve of PFS per IRRC, Secondary definition - All randomised subjects with OS at least 5 years with intermediate/poor risk**

**Figure 4 KM curve of post-response survival in subjects who achieved complete of partial response (per IRRC by treatment arm - CheckMate 214 intermediate/poor risk (60 month minimum follow-up)**

**Figure 5 KM curve of time from randomization to first subsequent systemic anticancer therapy - CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up)**

**Figure 6 KM curve of time from randomization to second subsequent systemic anticancer therapy - CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up)**

**Figure 7 OS extrapolations for the Company base case (log-normal) and ERG preferred scenarios – CheckMate 214 intermediate/poor-risk patients (60-month minimum DBL)**

**Figure 8: OS smoothed hazard plots of CheckMate 214 data from the 48-month minimum DBL (black) and 60-month minimum DBL (blue) with all patients censored from the time point indicated in the figure**

Black solid line = 48-month minimum DBL; blue dashed line = 60 month minimum DBL. Circles highlight end of smoothed hazard plots and pattern of change between plots by adding an additional month of data for patients. A 12-month smoothing interval was used for hazard plots.

Figure 9. OS smoothed hazard plots of CheckMate 214 data and corresponding KM data from A) 30-month minimum DBL, B) 42-month minimum DBL, C) 48-month minimum DBL, D) 60-month minimum DBL.

Note: Circles highlight pattern of smoothed hazard curves in heavily censored portion of the KM curve, with arrows indicating sunitinib hazard and corresponding KM data and numbers of patients at risk. A 12-month smoothing interval was used for hazard plots.

**Figure 10. OS smoothed hazard plots of CheckMate 214 data across 30-month minimum DBL 42-month minimum DBL, 48-month minimum DBL, 60-month minimum DBL**

Note: Vertical dashed lines represent minimum follow-up for corresponding DBL. A 12-month smoothing interval was used for hazard plots.

**Figure 11. Estimated hazard ratio and 95% CI for CheckMate 214 OS over 180 months (15 years)**

# References

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