# Horizon Scanning in Oncology

## Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC)

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 82
ISSN online 2076-5940

# Horizon Scanning in Oncology

## Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC)

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, August 2018

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Dr. med. Eleen Rothschedl
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc
External review: Dr. Kilian Gust, Univ. Klinik für Urologie, Allgemeines Krankenhaus der Stadt Wien – Medizinischer Universitätscampus

## DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

## CONTACT INFORMATION

**Publisher:**

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6. Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

**Responsible for contents:**

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessment.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at.

DSD: Horizon Scanning in Oncology No. 82
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with advanced RCC


## Abstract

### Introduction

Renal cell carcinomas (RCCs) arise from the renal cortex; many patients with RCC are asymptomatic until the disease is either locally advanced and unresectable, or metastatic. To date, nivolumab (Opdivo®), a human immunoglobulin G4 (Ig4) monoclonal antibody directed against programmed death-1 (PD-1), has not been approved throughout Europe for the treatment of patients with advanced RCC who did not receive prior treatment. Since April 2018, nivolumab in combination with ipilimumab (Yervoy®) has been approved in the US for the treatment of patients with intermediate- or poor-risk advanced RCC who did not receive prior therapy.

### Methodology

Published and grey literature were identified by searching the CRD Database, Embase, Ovid Medline and PubMed, Internet sites and contacting the manufacturer, resulting in 224 references overall. A quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity of randomised controlled trials. To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used. Additionally, an adapted version (due to perceived limitations) of ESMO-MCBS was applied.

### Results from the CheckMate 214 trial

The CheckMate 214 trial assessed the combination of nivolumab plus ipilimumab versus sunitinib (Sutent®) monotherapy in patients with previously untreated advanced RCC in 1,096 patients (79% of the overall study population had intermediate- or poor-risk RCC. Analyses showed that intermediate- and poor-risk patients who received nivolumab plus ipilimumab showed a statistically significant benefit in overall survival (OS) and objective response rate (ORR) as compared with sunitinib: the 12-month OS rate was 80% versus 72%, the 18-month OS rate was 75% versus 60%, with a hazard ratio (HR) for death of 0.63 (99.8% CI, 0.44–0.89; $p < 0.001$) and an ORR of 42% versus 27% ($p < 0.001$) in the respective groups. Health-related quality of life (HRQoL) analyses showed better results in intermediate- and poor-risk patients treated with nivolumab plus ipilimumab. Median progression-free survival (PFS) was prolonged with nivolumab plus ipilimumab, whereas the difference was not statistically significant. Treatment-related AEs of grade 3 or 4 occurred in 46% (nivolumab-plus-ipilimumab group) and 63% (sunitinib group) of patients. The number of treatment-related deaths was higher in patients receiving nivolumab plus ipilimumab.

### Conclusion

CheckMate 214 study results show that the combination of nivolumab and ipilimumab provides clinical benefit in previously untreated, intermediate- and poor-risk patients. However, the high rate of treatment-related AEs has to be considered. Moreover, data regarding AEs for intermediate- and poor-risk patients and, additionally, long-term efficacy and safety data of the combination therapy would be of interest. Since CheckMate 214 is the only phase III trial providing results of nivolumab plus ipilimumab in untreated patients with advanced RCC, more data is needed to evaluate this combination regimen for first-line therapy.

## Table of Contents



### List of tables

# 1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to predefined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA
HTA Core Model®

| Element ID | Research question |
|---|---|
| **Description of the technology** | |
| B0001 | What is nivolumab, ipilimumab and sunitinib? |
| A0022 | Who manufactures nivolumab? |
| A0007 | What is the target population in this assessment? |
| A0020 | For which indications has nivolumab received marketing authorisation? |
| **Health problem and current use** | |
| A0002 | What is renal cell carcinoma? |
| A0004 | What is the natural course of renal cell carcinoma? |
| A0006 | What are the consequences of renal cell carcinoma for the society? |
| A0023 | How many people belong to the target population? |
| A0005 | What are the symptoms and the burden of renal cell carcinoma? |
| A0003 | What are the known risk factors for renal cell carcinoma? |
| A0024 | How is renal cell carcinoma currently diagnosed according to published guidelines and in practice? |
| A0025 | How is renal cell carcinoma currently managed according to published guidelines and in practice? |
| **Clinical effectiveness** | |
| D0001 | What is the expected beneficial effect of nivolumab on mortality? |
| D0006 | How does nivolumab affect progression (or recurrence) of renal cell carcinoma? |
| D0005 | How does nivolumab affect symptoms and findings (severity, frequency) of renal cell carcinoma? |
| D0011 | What is the effect of nivolumab on patients' body functions? |
| D0012 | What is the effect of nivolumab on generic health-related quality of life? |
| D0013 | What is the effect of nivolumab on disease-specific quality of life? |
| **Safety** | |
| C0008 | How safe is nivolumab in relation to the comparator? |
| C0002 | Are the harms related to dosage or frequency of applying nivolumab? |
| C0005 | What are the susceptible patient groups that are more likely to be harmed through the use of nivolumab? |
| A0021 | What is the reimbursement status of nivolumab? |

# 2 Drug description

## Generic/Brand name/ATC code:

Nivolumab/Opdivo®/L01XC17

### B0001: What is nivolumab, ipilimumab and sunitinib?

nivolumab is an Ig4 antibody directed against PD-1

Nivolumab (Opdivo®) is a human immunoglobulin G4 (Ig4) monoclonal antibody which is directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1), showing immune checkpoint inhibitory and antineoplastic activities. Nivolumab binds to the PD-1 receptor, thereby blocking its interaction with programmed cell death ligand 1 (PD-L1) which is overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2) which is primarily expressed on antigen presenting cells (APCs). This mechanism leads to the inhibition of T-cell proliferation and cytokine secretion. By blocking PD-1 binding to PD-L1 and PD-L2 ligands, nivolumab intensifies T-cell responses, including anti-tumour responses [2, 3].

combination regimen: nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, then nivolumab as single agent for maintenance therapy

Nivolumab, which is produced in Chinese hamster ovary cells by recombinant deoxyribonucleic acid (DNA) technology is available as a concentrate for solution for infusion in vials of 4 mL, 10 mL and 24 ml (each mL contains 10 mg of nivolumab) [2]. The U.S. Food and Drug Administration (FDA) recommends administering nivolumab (if given in combination with ipilimumab) at a dose of 3 mg/kg intravenously (IV) over 30 minutes, followed by ipilimumab at a dose of 1 mg/kg IV over 30 minutes on the same day, every three weeks for four doses (induction phase). After completion of the combination regimen, the administration of nivolumab as a single agent (either 240 mg every two weeks or 480 mg every four weeks IV over 30 minutes) is recommended until disease progression or unacceptable toxicity (maintenance phase) [4].

corticosteroids and immunosuppres-sants should be avoided prior to treatment

Before starting the administration of nivolumab, the use of systemic corticosteroids and other immunosuppressants should be avoided, since they could potentially interfere with the pharmacodynamic activity. After starting nivolumab therapy, systemic corticosteroids and immunosuppressants can be used for the treatment of immune-related adverse reactions [2].

ipilimumab: anti-CTLA-4 antibody

Ipilimumab (Yervoy®) is a human anti-cytotoxic T-lymphocyte-associated (CTLA)-4 monoclonal antibody (IgG1κ) [5]. The recommended dose for the treatment of advanced renal cell carcinoma (RCC) is 3 mg/kg of nivolumab administered IV over 30 minutes followed by 1 mg/kg of ipilimumab administered IV over 30 minutes on the same day, every 3 weeks for a maximum of 4 doses, then 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks, administered IV over 30 minutes [6]. Ipilimumab can cause severe and fatal immune-mediated adverse reactions; most commonly including enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy and endocrinopathy. If a severe immune-mediated adverse reaction occurs, ipilimumab must be discontinued permanently and a systemic high-dose corticosteroid therapy must be administered. Patients must be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrino-

warning of severe and fatal immune-mediated adverse reactions

pathy. At baseline and before each dose of ipilimumab, an evaluation of clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level and thyroid function tests should be conducted [6]. With reference to combination therapy, immune-related adverse reactions occurred more often when nivolumab was administered in combination with ipilimumab compared to nivolumab monotherapy [5].

sunitinib: oral inhibitor of multiple RTKs

Sunitinib (Sutent®) is an inhibitor of multiple receptor tyrosine kinases (RTKs); it is indicated for the treatment of advanced/metastatic renal cell carcinoma (RCC) in adult patients. The recommended dose of sunitinib for the treatment of metastatic RCC is 50 mg per day for four consecutive weeks, followed by a two-week rest period, adding up to a complete cycle of six weeks. Sunitinib is available as hard capsules for oral administration. The most serious adverse reactions (some of them fatal) associated with the administration of sunitinib are renal or heart failure, pulmonary embolism, gastrointestinal perforation and haemorrhages; the most common adverse reactions of any grade are decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders, skin discolouration and palmar-plantar erythrodysesthesia syndrome. Furthermore, hypothyroidism or haematological disorders may develop during sunitinib treatment. Fatal events that were considered to be possibly related to the administration of sunitinib included multisystem organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, adrenal insufficiency, pneumothorax, shock and sudden death [7].

**A0022: Who manufactures nivolumab?**

Bristol-Myers Squibb

# 3 Indication

**A0007: What is the target population in this assessment?**

first-line therapy for patients with advanced RCC

Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) is indicated in patients with previously untreated advanced RCC with a clear-cell component.

# 4 Current regulatory status

**A0020: For which indications has nivolumab received marketing authorisation?**

currently not approved for untreated RCC by the EMA

In June 2015, the European Medicines Agency (EMA) initially granted marketing authorisation for nivolumab (Opdivo®) for the treatment of advanced (unresectable or metastatic) melanoma in adults. To date, nivolumab has not been approved for the treatment of patients with untreated advanced RCC. Nivolumab has been approved by the EMA for the following indications [8]:

approved indications in Europe

- As monotherapy for the treatment of advanced RCC after prior therapy in adults.
- As monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab has been established only in patients with low tumour PD-L1 expression. According to Opdivo® label information [2], before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy.
- As monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.
- As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.
- As monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.
- For the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

04/2018: FDA approval of nivolumab + ipilimumab for untreated, advanced RCC

In April 2018, the FDA approved nivolumab in combination with ipilimumab for the treatment of patients with intermediate- or poor-risk advanced RCC who had not received prior therapy. In the US, nivolumab is also approved for the following indications [9]:

approved indications in the US

- In patients with advanced RCC who have received prior anti-angiogenic therapy.
- As a single agent for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma and in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (accelerated approval based on PFS).
- In patients with unresectable or metastatic melanoma, in combination with ipilimumab (accelerated approval based on PFS).

- In patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- For the treatment of patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- In adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous haematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or three or more lines of systemic therapy that includes autologous HSCT. Both indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR).
- For the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy.
- In patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within twelve months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Both indications are approved under accelerated approval based on ORR and DOR data.
- In adult and paediatric (twelve years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan (under accelerated approval based on ORR and DOR data).
- For the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (under accelerated approval based on ORR and DOR data).

# 5 Burden of disease

### A0002: What is renal cell carcinoma?

RCCs arise from the renal cortex

histologically, clear-cell pattern is most common

80% to 85% of all primary renal neoplasms are RCCs that originate within the renal cortex. Histologically, the majority of RCCs have a clear-cell component (75–85% of tumours); less common subtypes of RCCs are papillary carcinomas, chromophobe carcinomas, oncocytomas, collecting duct (Bellini's duct) tumours and translocation carcinomas. Clear-cell carcinomas arise from the proximal tubule and are macroscopically solid or – less common – cystic. Typically, RCCs with a clear-cell component have a deletion of chromosome 3p [10].

### A0004: What is the natural course of renal cell carcinoma?

often diagnosed at an advanced stage

Many patients with RCC are asymptomatic until the disease is either locally advanced and unresectable, or metastatic. Although surgical resection can be curative in patients with localised disease, many patients who are resectable may eventually recur. Generally, the prognosis for long-term disease-free survival is poor, the same accounts for patients with locally advanced or metastatic disease [11].

RCC: 5-year relative survival rate is 76.2%

In Austria, the relative survival rate following diagnosis in patients with RCC (2008–2012) is 84.9% at one year, 79.2% at three years and 76.2% at five years. The age-standardised mortality rate for the European Standard Population for RCC (2015) is 7.3 per 100,000 per year in men and 3.4 per 100,000 per year in women [12].

### A0006: What are the consequences of renal cell carcinoma for the society?

### A0023: How many people belong to the target population?

Austria: 1,258/year newly diagnosed with RCC

The median age of diagnosis of RCC is 67 years in men and 72 years in women [13]. According to data from the US (2011–2015), the median age at diagnosis of kidney and renal pelvis cancer is 64 years [14].

median age at diagnosis of RCC: 64 years

In Austria, 1,258 persons per year (2015) are newly diagnosed with RCC which is more frequent in men than in women, with 813 newly diagnosed men compared to 445 newly diagnosed women per year (2015). The age-standardised incidence rate for the European Standard Population for RCC (2015) is 21.1 per 100,000 per year in men and 9.6 per 100,000 per year in women [12]. Since approximately 25% of patients have distant metastases or advanced locoregional disease at the time of presentation [11], the target population in Austria includes approximately 315 persons per year.

### A0005: What are the symptoms and the burden of renal cell carcinoma?

often asymptomatic until advanced disease stage

>50% of RCC cases are detected incidentally

classical triad: flank pain, flank mass, haematuria

paraneoplastic symptoms

Patients with RCC can present with a range of symptoms. However, many patients are asymptomatic until the disease is at an advanced stage and more than 50% of RCC cases are detected incidentally [15]. The classical triad symptoms of flank pain, haematuria and palpable abdominal renal mass – strongly suggesting locally advanced disease – are thus found less frequently. Symptoms that may result from metastatic disease include: haematuria, which occurs when the tumour affects the collecting system, involvement of the vena cava that can lead to lower extremity oedema, ascites, hepatic dysfunction and pulmonary emboli. Scrotal varicoceles (mostly left-sided) can be found in as many as 11% of men affected by RCC. In patients with disseminated disease the most common involved sites include the lungs, lymph nodes, bones, liver and brain; symptoms include bone pain, adenopathy and pulmonary symptoms. Possible paraneoplastic symptoms are anaemia, hepatic dysfunction, fever (in up to 20% of patients), hypercalcaemia (in up to 15% of patients with advanced disease), cachexia, erythrocytosis, secondary amyloidosis, thrombocytosis, and polymyalgia rheumatica. The occurrence of RCC in patients that are ≤46 years may indicate an inheritable disease that should be further evaluated [11, 15, 16].

### A0003: What are the known risk factors for renal cell carcinoma?

established risk factors: smoking, hypertension and obesity

There are several established risk factors for the development of RCCs, including cigarette smoking and hypertension. Another risk factor is obesity, since the relative risk of RCC increases progressively with the baseline body mass index (BMI). Additionally, the following factors that lead to chronic renal failure can increase the risk of developing RCC: an acquired cystic disease of the kidney (in approximately 35–50% of chronic dialysis patients from whom approximately 6% eventually develop RCC), an occupational exposure to toxic compounds (e.g. cadmium, asbestos, petroleum by-products) and the prolonged ingestion of analgesic combinations. Patients who have been initially treated for renal cancer have an increased risk of developing a second, metachronous RCC. Moreover, the use of cytotoxic chemotherapy in childhood has been associated with the subsequent development of translocation carcinomas. Further established risk factors for RCC are a chronic hepatitis C infection, sickle cell disease (risk of renal medullary carcinoma) and a history of kidney stones [10]. Approximately 2–3% of all RCCs are hereditary and associated with several autosomal dominant syndromes [15]; clear-cell carcinomas are specifically associated with von-Hippel-Lindau disease [10].

2–3% of RCCs are hereditary

### A0024: How is renal cell carcinoma currently diagnosed according to published guidelines and in practice?

physical examination, medical history evaluation, laboratory examinations

When RCC is suspected, an initial physical examination and evaluation of the patient's medical history should be performed. Laboratory examinations including serum creatinine, haemoglobin, leukocyte and platelet counts, lymphocyte-to-neutrophil ratio, lactate dehydrogenase, C-reactive protein (CRP) and serum-corrected calcium, as well as other symptom-derived tests are necessary. Patients affected by RCC typically present with a suspicious mass involving the kidney which is usually detected by a radiographic study. A computed tomography (CT) enables assessment of local invasiveness, involvement of lymph nodes or the presence of distant metastases. Additional information regarding local advancement and venous involvement can be yielded by the use of magnetic resonance imaging (MRT). Contrast-enhanced chest, abdominal and pelvic CT is mandatory for the staging of RCC. For routine clinical practice, the use of a bone scan or CT/MRT of the brain is not recommended, unless it is indicated by clinical or laboratory signs or symptoms. The European Society for Medical Oncology (ESMO) recommends a renal core biopsy to confirm malignancy before treatment with ablative therapies and in patients with metastatic disease prior to starting systemic treatment. Finally, histopathological diagnosis, classification, grading and evaluation of prognostic factors can be based on the specimen obtained by nephrectomy [15, 16].

CT, optional MRT

specimen can be obtained by nephrectomy

IMDC: favourable, intermediate or unfavourable/poor risk

To determine the prognosis of patients with metastatic disease, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is used to classify the patient's risk as favourable, intermediate or unfavourable/poor. The prognostic model comprises six factors: Karnofsky performance status (PS) <80%, haemoglobin under the lower limit of normal, time from diagnosis to treatment of <1 year, corrected calcium above the upper limit of normal (ULN), platelets greater than the ULN, and neutrophils greater than the ULN [15].

# 6 Current treatment

**A0025: How is renal cell carcinoma currently managed according to published guidelines and in practice?**

**ESMO treatment recommendations for metastatic RCC**

According to ESMO [15], the following options for the treatment of metastatic RCC are recommended:

- Regarding local therapy and surgery, cytoreductive nephrectomy is only recommended in patients having a good PS and large primary tumours with limited volume of metastatic disease as well as in patients with a symptomatic primary lesion.
- For selected patients, metastasectomy and other local treatment strategies (e.g. whole-brain radiotherapy, conventional radiotherapy, stereotactic radiosurgery, stereotactic body radiotherapy, cyberknife radiotherapy, and hypofractionated radiotherapy) can be considered after multidisciplinary review.

For systemic treatment in patients with good or intermediate risk, ESMO recommends:

- First-line:
  - sunitinib
  - bevacizumab + interferon
  - pazopanib
  - optional: high-dose interleukin-2, sorafenib, bevacizumab + low-dose interferon
- Second-line (post cytokines):
  - axitinib
  - sorafenib
  - pazopanib
  - optional: sunitinib
- Third-line treatment after two tyrosine kinase inhibitors (TKIs):
  - nivolumab
  - cabozantinib
  - optional: everolimus
- Third-line treatment after TKI and mammalian target of rapamycin (mTOR):
  - sorafenib
  - nivolumab
  - cabozantinib
  - optional: other TKI or rechallenge.

For systemic treatment of patients with poor risk, recommended therapy options are:

- First-line treatment:
  - temsirolimus
  - optional: sunitinib, sorafenib, pazopanib
- Second-line treatment (post-TKIs):

- nivolumab
- cabozantinib
- optional: axitinib, everolimus, sorafenib

❂ Third-line treatment (after TKI/nivolumab):
- cabozantinib
- optional: axitinib, everolimus

❂ Third-line treatment (after TKI/cabozantinib):
- nivolumab
- optional: everolimus, axitinib [15].

EAU recommendation

According to their updated guidelines [17], the European Association of Urology (EAU) strongly recommends to offer ipilimumab plus nivolumab for treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC. However, according to the EMA, nivolumab is indicated as monotherapy for the treatment of advanced RCC after prior therapy in adults and the assessed treatment option has not yet been approved.

# 7 Evidence

systematic literature search in 4 databases: 196 hits

A literature search was conducted on 13 June 2018 in four databases: CRD Database, Embase, Ovid Medline and PubMed. Search terms were “nivolumab”, “opdivo”, “ipilimumab”, “mdx1106”, “renal cell carcinoma”, “kidney cancer” and “advanced”. Also, the manufacturer was contacted, who submitted four references (three of them had already been identified by systematic literature search) as well as additional safety data. A manual search identified 28 additional references (web documents and journal articles).

manual search: 28 additional references

Overall, 224 references were identified. Included in this reported are:

overall: 224 references included: 2 studies

❂ a randomised, open-label phase III trial, comparing nivolumab plus ipilimumab versus sunitinib monotherapy in untreated patients with advanced renal cell carcinoma [18].

❂ an open-label, parallel-cohort, dose-escalation phase I study to evaluate the efficacy and safety of nivolumab plus ipilimumab or nivolumab and a TKI in patients with mRCC [19].

study-level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity of randomised controlled trials (RCTs) [20]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patients and treating physicians, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 6 (see appendix).

applicability of study results

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting (see Table 5) [21].

**magnitude of meaningful clinical benefit assessed based on ESMO-MCBS**

To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [22]. Additionally, an adapted version (due to perceived limitations) of ESMO-MCBS was applied [23]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

## 7.1 Quality assurance

**internal and external review**

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

**quality assurance method**

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

## 7.2. Clinical efficacy and safety – phase III study

**CheckMate 214: randomised, open-label phase III trial**

CheckMate 214 [18, 24, 25] is a randomised, open-label phase III trial evaluating the efficacy and safety of nivolumab plus ipilimumab versus sunitinib. For that reason, a total of 1,096 patients were randomly assigned between October 2014 and February 2016 at 175 sites in 28 countries throughout Asia, Europe, Australia and America. Included patients had to have previously untreated advanced RCC with a clear-cell component. According to IMDC, 425 patients treated with nivolumab plus ipilimumab and 422 patients treated with sunitinib had intermediate- or poor-risk RCC (79% of the overall study population), respectively. IMDC intermediate- and poor-risk patients had a median age of 62 years in the nivolumab-plus-ipilimumab group and 61 years in the sunitinib group. 26% of patients in the nivolumab-plus-ipilimumab group and 29% of patients in the sunitinib group were fe-

**patient characteristics**

male. 79% (nivolumab-plus-ipilimumab group) and 80% (sunitinib group) of patients with IMDC intermediate or poor risk had two or more sites with target or non-target lesions. 80% of patients of the nivolumab-plus-ipilimumab group and 76% of patients of the sunitinib group had previously undergone nephrectomy, 12% of patients of both groups had previously received radiotherapy. 74% of patients receiving nivolumab plus ipilimumab and 71% of sunitinib group patients showed less than 1% of quantifiable tumour PD-L1 expression. The most common sites of metastasis among patients of both groups were the lung and lymph nodes. Baseline demographic and clinical characteristics were similar in patients of the intention-to-treat (ITT) population that included patients with favourable, intermediate or poor risk. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 5.

nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks

Patients received nivolumab IV at a dose of 3 mg/kg over a period of 60 minutes and ipilimumab at a dose of 1 mg/kg over a period of 30 minutes, both every three weeks for four doses during the induction phase. In the subsequent maintenance phase, nivolumab monotherapy was administered at a dose of 3 mg/kg every two weeks. Patients of the sunitinib group received their study drug at a dose of 50 mg orally once daily for four weeks of each six-week cycle.

sunitinib: 50 mg once daily for 4 weeks

The co-primary endpoints of the CheckMate 214 trial were ORR, PFS and overall survival (OS) among intermediate- or poor-risk patients. Secondary endpoints were ORR, PFS and OS in the ITT population as well as the incidence rate of adverse events (AEs) among all treated patients. Exploratory endpoints were ORR, PFS and OS in patients with IMDC favourable risk. Additional exploratory endpoints were health-related quality of life (HRQoL) and outcomes according to the level of tumour PD-L1 expression.

co-primary endpoints: ORR, PFS, OS among intermediate- and poor-risk patients

Database lock was on 7 August 2017; at that time, 23% in the nivolumab-plus-ipilimumab group and 18% of patients in the sunitinib group continued treatment. In patients who discontinued treatment, the most common reason for discontinuation was disease progression with 42% of patients in the nivolumab-plus-ipilimumab group and 55% of patients in the sunitinib group. Less common reasons were study drug toxicities and AEs unrelated to the study drug.

treatment discontinuation in 42% (nivolumab-plus-ipilimumab group) and 55% (sunitinib group)

The median follow-up in the CheckMate 214 trial was 25.2 months, with a minimum follow-up of 17.5 months. The median duration of treatment in patients receiving nivolumab plus ipilimumab was 7.9 months (95% confidence interval, CI, 6.5–8.4) and 7.8 months (95% CI, 6.4–8.5) in patients of the sunitinib group. 79% of patients received all four doses of nivolumab plus ipilimumab. 39% of patients in the nivolumab-plus-ipilimumab group received subsequent systemic therapy, most commonly with sunitinib and pazopanib. Among sunitinib group patients, 54% received subsequent systemic therapy, with nivolumab and axitinib being administered most frequently.

median duration of treatment: 7.9 months (nivolumab + ipilimumab) vs. 7.8 months (sunitinib group)

permission to cross over after primary endpoint was met

According to a protocol amendment in November 2017, patients were permitted to cross over from the sunitinib group to the nivolumab-plus-ipilimumab group after the primary endpoint had been met. It is worthy of note that the CheckMate 214 trial is currently ongoing, with an estimated study completion date of September 2019.

CheckMate 214: ongoing until 09/2019

## 7.2.1 Clinical efficacy

**D0001: What is the expected beneficial effect of nivolumab on mortality?**

**nivolumab + ipilimumab: statistically significant OS benefit in intermediate- and poor-risk patients**

OS in intermediate- and poor-risk patients (n = 847) was a co-primary endpoint in the CheckMate 214 trial. Efficacy analyses showed a statistically significant OS benefit in patients receiving nivolumab plus ipilimumab over patients who received sunitinib. The 12-month OS rate was 80% (95% CI, 76–84) in patients of the nivolumab-plus-ipilimumab group versus 72% (95% CI, 67–76) in patients of the sunitinib group. 18-month OS rates were 75% (95% CI, 70–78) in patients receiving nivolumab plus ipilimumab versus 60% (95% CI, 55–65) in sunitinib group patients with a hazard ratio (HR) for death of 0.63 (99.8% CI, 0.44–0.89; p <0.001). Median OS was not reached (95% CI, 28.2 months–NE[1]) in patients of the nivolumab-plus-ipilimumab group and was 26.0 months (95% CI, 22.1–NE) in patients receiving sunitinib. The OS benefit of nivolumab plus ipilimumab was shown across all subgroups; even if its extent differed among the subgroups.

**nivolumab + ipilimumab: statistically significant OS benefit in the ITT population**

OS in the ITT population (n = 1096) was a secondary endpoint; the 12-month OS rate and the 18-month OS rate were 83% (95% CI, 80–86) and 78% (95% CI, 74–81) in patients of the nivolumab-plus-ipilimumab group versus 77% (95% CI, 74–81) and 68% (95% CI, 63–72) in patients of the sunitinib group, respectively. Median OS was not reached in patients who received nivolumab plus ipilimumab and was 32.9 months in patients who received sunitinib. The OS benefit was statistically significantly higher in the nivolumab-plus-ipilimumab group compared to the sunitinib group: HR for death was 0.68 (99.8% CI, 0.49–0.95; p <0.001).

**favourable-risk patients: better results when treated with sunitinib**

The 12-month OS rate and the 18-month OS rate of favourable-risk patients (n = 249) was 94% (95% CI, 87–97) and 88% (95% CI, 80–92) in patients treated with nivolumab plus ipilimumab versus 96% (95% CI, 90–98) and 93% (95% CI, 87–97) in patients receiving sunitinib, respectively. With 1.45 (99.8% CI, 0.51–4.12; p = 0.27), HR for death favoured sunitinib treatment. Median OS was not reached in patients of the nivolumab-plus-ipilimumab group and was 32.9 months (95% CI, NE) in the sunitinib group. At the time of database lock (August 7, 2017), 37 deaths had occurred in this subpopulation.

**exploratory analyses: prolonged OS in intermediate- and poor-risk patients who had quantifiable PD-L1 expression**

Exploratory analyses showed that among the 776 intermediate- and poor-risk patients who had quantifiable PD-L1 expression, OS was longer across PD-L1 expression levels in patients receiving nivolumab plus ipilimumab than in patients receiving sunitinib. In patients with PD-L1 expression less than 1%, the 12-month and the 18-month OS rates were 80% (95% CI, 75–84) and 74% (95% CI, 69–79) in patients of the nivolumab-plus-ipilimumab group versus 75% (95% CI, 70–80) and 64% (95% CI, 58–70) in patients of the sunitinib group. In both groups, median OS was not reached; HR for death was 0.73 (95% CI, 0.56–0.96).

**PD-L1 expression ≥1%: higher OS rates with nivolumab-plus-ipilimumab**

In patients with PD-L1 expression of 1% or greater (n = 214), the 12-month and the 18-month OS rates were 86% (95% CI, 77–91) and 81% (95% CI, 71–87) in patients receiving nivolumab plus ipilimumab compared to 66% (95% CI, 56–74) and 53% (95% CI, 43–62) in patients receiving sunitinib. Median OS was not reached in the nivolumab-plus-ipilimumab group and was 19.6

[1] NE = not estimable

months (95% CI, 14.8–NE) in the sunitinib group, resulting in a HR for death of 0.45 (95% CI, 0.29–0.71).

### D0006: How does nivolumab affect progression (or recurrence) of renal cell carcinoma?

PFS in intermediate- and poor-risk patients (n = 847) was a co-primary endpoint in the CheckMate 214 trial; median PFS was 11.6 months (95% CI, 8.7–15.5) in patients of the nivolumab-plus-ipilimumab group versus 8.4 months (95% CI, 7.0–10.8) in sunitinib group patients. However, the between-group difference (HR for disease progression or death of 0.82, 99.1% CI, 0.64–1.05, p = 0.03) did not meet the pre-specified threshold of p = 0.009 and thereby fails to be of statistical significance.

intermediate-/poor-risk patients: PFS with nivolumab + ipilimumab improved, but not statistically significantly

Among patients of the ITT population (n = 1096), PFS did not differ statistically significantly either between patients receiving nivolumab plus ipilimumab and patients receiving sunitinib (HR for disease progression or death of 0.98, 99.1% CI, 0.79–1.23; p = 0.85). Median PFS was 12.4 months (95% CI, 9.9–16.5) in patients of the nivolumab-plus-ipilimumab group and 12.3 months (95% CI, 9.8–15.2) in patients of the sunitinib group.

ITT population: no statistically significant difference

In patients with IMDC favourable risk (n = 249), median PFS was 15.3 months (95% CI, 9.7–20.3) in the nivolumab-plus-ipilimumab group and 25.1 months (95% CI, 20.9–NE) with a HR of 2.18 (99.1% CI, 1.29–3.68; p <0.001), in favour of the sunitinib group.

favourable-risk patients: PFS in favour of sunitinib

Patients with a PD-L1 expression level of lower than 1% (n = 562) had a median PFS of 11.0 months (nivolumab-plus-ipilimumab group) versus 10.4 months (sunitinib group), resulting in a HR for disease progression or death of 1.00 (95% CI, 0.80–1.26). Patients showing a PD-L1 expression of 1% or greater (n = 214) had a median PFS of 22.8 months in patients receiving nivolumab plus ipilimumab and 5.9 months in patients receiving sunitinib (HR for disease progression or death of 0.46, 95% CI, 0.31–0.67).

PD-L1 expression <1%: +0.6 months median PFS

PD-L1 expression ≥1%: +16.9 months median PFS

### D0005: How does nivolumab affect symptoms and findings (severity, frequency) of renal cell carcinoma?

ORR was another co-primary endpoint of the CheckMate 214 trial. In the intermediate- and poor-risk subpopulation (n = 847) analyses have shown an ORR of 42% (95% CI, 37–47) in patients receiving nivolumab plus ipilimumab versus 27% (95% CI, 22–31) in patients receiving sunitinib (p <0.001). Of all intermediate- and poor-risk patients who received nivolumab plus ipilimumab, 9%, 32%, 31% and 20% achieved complete response (CR), partial response (PR), stable disease and progressive disease, respectively. Intermediate- and poor-risk patients of the sunitinib group achieved CR, PR, stable disease and progressive disease in 1%, 25%, 45% and 17%, respectively. The median time to response was 2.8 months (ranging from 0.9 to 11.3 months) in patients of the nivolumab-plus-ipilimumab group and 3.0 months (ranging from 0.6 to 15.0 months) in patients of the sunitinib group. 81% of all patients with intermediate- or poor-risk RCC who received nivolumab plus ipilimumab and 70% of patients who were treated with sunitinib showed a duration of response of at least one year. Overall, the median duration of response was not reached among patients of the nivolumab-plus-ipilimumab group (95% CI, 21.8 months–NE); patients of the sunitinib group had a median duration of response of 18.2 months (95%

intermediate- or poor-risk patients: ORR 42% with nivolumab + ipilimumab vs. 27% with sunitinib

CI, 14.8 months–NE). Data from the first interim analyses showed that 72% of patients treated with nivolumab plus ipilimumab and 63% of patients who received sunitinib had an ongoing response.

ITT population: difference not statistically significant

Among patients of the ITT population (n = 1096), ORR was 39% (95% CI, 35–43) in patients of the nivolumab-plus-ipilimumab group and 32% (95% CI, 28–36) in patients who received sunitinib, resulting in p = 0.02, which is not statistically significant regarding the pre-specified threshold of p = 0.001.

favourable-risk patients: statistically significant improvement in sunitinib patients

Among favourable-risk patients (n = 249), ORR was 29% (95% CI, 21–38) in patients treated with nivolumab plus ipilimumab compared to 52% (95%CI 43–61) in patients who were treated with sunitinib (p <0.001). The rate of CR was 11% in patients of the nivolumab-plus-ipilimumab group and 6% in patients of the sunitinib group.

improved ORR independent of PD-L1 expression

In patients with a PD-L1 expression lower than 1% (n = 562), ORR was 37% in patients of the nivolumab-plus-ipilimumab group versus 28% in patients of the sunitinib group (p = 0.03). Patients showing a PD-L1 expression of 1% or greater (n = 214) had an ORR of 58% (nivolumab-plus-ipilimumab group) versus 22% (sunitinib group), resulting in a statistically significant difference (p <0.001).

### D0011: What is the effect of nivolumab on patients' body functions?

better HRQoL reported by nivolumab-plus-ipilimumab-group patients

Based on analyses of the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), patients who received nivolumab plus ipilimumab reported better HRQoL than patients treated with sunitinib. Items of FKSI-19 include pain, fatigue, pulmonary symptoms, bowel/bladder symptoms, nutritional health, psychosocial functioning and treatment side effects. Detailed information regarding HRQoL of patients participating in the CheckMate 214 trial is presented below.

### D0012: What is the effect of nivolumab on generic health-related quality of life?

<80% in both groups completed FKSI-19

HRQoL was assessed by using FKSI-19; the rate of completion of the FKSI-19 questionnaire was higher than 80% in patients of either group during the first six months. Analyses showed that, among intermediate- and poor-risk patients, the mean change from baseline at each assessment during the first six months was greater in patients who were treated with nivolumab plus ipilimumab than in patients treated with sunitinib (p <0.001). The descriptive results are substantiated by both the pattern-mixture model (a flexible and transparent way to analyse incomplete longitudinal data where the missingness is non-ignorable [26]) and the mixed-model repeated measures (a specialised mixed-model procedure that analyses results from repeated measures designs in which the outcome (response) is continuous and measured at fixed time points [27]), indicating a significant difference in favour of patients treated with nivolumab plus ipilimumab [18].

mean change from baseline greater in patients treated with nivolumab + ipilimumab

benefits observed throughout the treatment

The assessed benefits in HRQoL of nivolumab plus ipilimumab over sunitinib were observed early during the induction phase and were generally maintained throughout the treatment including the nivolumab maintenance phase. Also, the benefits were apparent overall and across most domains of

disease-related symptoms of kidney cancer (FKSI-19), general cancer (HRQoL) and health status (EQ-5D-3L) [28].

### D0013: What is the effect of nivolumab on disease-specific quality of life?

No evidence was found to answer this research question.

*Table 1: Efficacy results of the CheckMate 214 trial [18, 24]*

| Descriptive statistics and estimate variability | Treatment group | Nivolumab + ipilimumab | Sunitinib |
|---|---|---|---|
| | **Number of patients** | | |
| | Intermediate- and poor-risk patients | 425 | 422 |
| | ITT population | 550 | 546 |
| | Favourable-risk patients | 125 | 124 |
| | Patients with quantifiable PD-L1 expression[1] | 384 | 392 |
| | PD-L1 expression ≥1% | 100 | 114 |
| | PD-L1 expression <1% | 284 | 278 |
| | **OS** | | |
| | **Intermediate- and poor-risk patients** | | |
| | 12-month OS rate, % (95% CI) | 80 (76–84) | 72 (67–76) |
| | 18-month OS rate, % (95% CI) | 75 (70–78) | 60 (55–65) |
| | Median OS, months (95% CI) | NR (28.2–NE) | 26.0 (22.1–NE) |
| | **ITT population** | | |
| | 12-month OS rate, % (95% CI) | 83 (80–86) | 77 (74–81) |
| | 18-month OS rate, % (95% CI) | 78 (74–81) | 68 (63–72) |
| | Median OS, months | NR | 32.9 |
| | **Favourable-risk patients** | | |
| | 12-month OS rate, % (95% CI) | 94 (87–97) | 96 (90–98) |
| | 18-month OS rate, % (95% CI) | 88 (80–92) | 93 (87–97) |
| | Median OS, months (95% CI) | NR | 32.9 (NE) |
| | **Patients with PD-L1 <1%** | | |
| | 12-month OS rate, % (95% CI) | 80 (75–84) | 75 (70–80) |
| | 18-month OS rate, % (95% CI) | 74 (69–79) | 64 (58–70) |
| | Median OS, months | NR | NR |
| | **Patients with PD-L1 ≥ 1%** | | |
| | 12-month OS rate, % (95% CI) | 86 (77–91) | 66 (56–74) |
| | 18-month OS rate, % (95% CI) | 81 (71–87) | 53 (43–62) |
| | Median OS, months (95% CI) | NR | 19.6 (14.8–NE) |
| | **PFS** | | |
| | **Intermediate- and poor-risk patients** | | |
| | Median PFS, months (95% CI) | 11.6 (8.7–15.5) | 8.4 (7.0–10.8) |
| | **PFS in ITT population** | | |
| | Median PFS, months (95% CI) | 12.4 (9.9–16.5) | 12.3 (9.8–15.2) |
| | **Favourable-risk patients** | | |
| | Median PFS, months (95% CI) | 15.3 (9.7–20.3) | 25.1 (20.9–NE) |
| | PD-L1 <1%, median PFS, months | 11.0 | 10.4 |
| | PD-L1 ≥1%, median PFS, months | 22.8 | 5.9 |

| | | | |
|---|---|---|---|
| | **ORR** | | |
| | **Intermediate- and poor-risk patients, %** | | |
| | Confirmed ORR, % (95% CI) | 42 (37–47) | 27 (22–31) |
| | **Confirmed best OR, %** | | |
| | CR | 9 | 1 |
| | PR | 32 | 25 |
| | Stable disease | 31 | 45 |
| | Progressive disease | 20 | 17 |
| | Unable to determine or not reported | 8 | 12 |
| | Median time to response, months (range) | 2.8 (0.9–11.3) | 3.0 (0.6–15.0) |
| | Median duration of response, months (95% CI) | NR (21.8–NE) | 18.2 (14.8–NE) |
| | Patients with ongoing response, % | 72 | 63 |
| | ORR in ITT population, % (95% CI) | 39 (35–43) | 32 (28–36) |
| | ORR in favourable-risk patients, % (95% CI) | 29 (21–38) | 52 (43–61) |
| | ORR in patients with | | |
| | PD-L1 <1%, % (95% CI) | 37 (32–43) | 28 (23–34) |
| | PD-L1 ≥1%, % (95% CI) | 58 (48–68) | 22 (15–31) |
| **Effect estimate per comparison** | *Comparison groups* | | Nivolumab + ipilimumab versus sunitinib |
| | **OS** | HR | 0.63 |
| | Intermediate- and poor-risk patients | 99.8% CI | 0.44–0.89 |
| | | p-value | <0.001 |
| | ITT population | HR | 0.68 |
| | | 99.8% CI | 0.49–0.95 |
| | | p-value | <0.001 |
| | Favourable-risk patients | HR | 1.45 |
| | | 99.8% CI | 0.51–4.12 |
| | | p-value | 0.27 |
| | PD-L1 <1% | HR | 0.73 |
| | | 95% CI | 0.56–0.96 |
| | | p-value | NA |
| | PD-L1 ≥1% | HR | 0.45 |
| | | 95% CI | 0.29–0.71 |
| | | p-value | NA |
| | **PFS** | HR | 0.82 |
| | Intermediate- and poor-risk patients | 99.1% | 0.64–1.05 |
| | | p-value | 0.03 |
| | ITT population | HR | 0.98 |
| | | 99.1% CI | 0.79–1.23 |
| | | p-value | 0.85 |
| | Favourable-risk patients | HR | 2.18 |
| | | 99.1% CI | 1.29–3.68 |
| | | p-value | <0.001 |
| | PD-L1 <1% | HR | 1.00 |
| | | 95% CI | 0.80–1.26 |
| | | p-value | NA |
| | PD-L1 ≥1% | HR | 0.46 |
| | | 95% CI | 0.31–0.67 |
| | | p-value | NA |
| | **ORR** | | |
| | Intermediate- and poor-risk patients | p-value | <0.001 |
| | ITT patients | p-value | 0.02 |
| | Favourable-risk patients | p-value | <0.001 |
| | Patients with PD-L1 <1% | p-value | 0.03 |
| | Patients with PD-L1 ≥1% | p-value | <0.001 |
| | HRQoL | p-value | <0.001 |

*Abbreviations: CI = confidence interval, CR = complete response, HR = hazard ratio, HRQoL = health-related quality of life, ITT = intention to treat, NA = not available, NE = not estimable, NR = not reached, OR = overall response, ORR = objective response rate, OS = overall survival, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, PR = partial response*

[1]*among 776 intermediate- and poor-risk patients*

## 7.2.2 Safety

**C0008: How safe is nivolumab in relation to the comparator?**

In 93% of nivolumab-plus-ipilimumab group patients and 97% of sunitinib group patients, treatment-related AEs of any grade occurred; grade 3 or 4 treatment-related AEs were reported in 46% (nivolumab-plus-ipilimumab group) and 63% (sunitinib group) of patients.

treatment-related AEs of grade 3 or 4 in 46% (nivolumab-plus-ipilimumab group) and 63% (sunitinib group)

In patients of the nivolumab-plus-ipilimumab group, the most frequent treatment-related grade 3 or 4 AEs occurring in 15% or more of treated patients were an increased lipase level, fatigue and diarrhoea, while hypertension, fatigue and palmar-plantar erythrodysesthesia occurred most commonly in the sunitinib group. 22% of nivolumab-plus-ipilimumab group patients and 12% of sunitinib group patients discontinued study treatment due to treatment-related AEs. Among patients of the nivolumab-plus-ipilimumab group, eight treatment-related deaths were reported; one each due to pneumonitis, pneumonia and aplastic anaemia, immune-mediated bronchitis, lower gastrointestinal haemorrhage, haemophagocytic syndrome, sudden death, liver toxic effects and lung infection. In the sunitinib group, four treatment-related deaths occurred, two of them caused by cardiac arrest and one each due to heart failure and multiple organ failure.

most frequent AEs with nivolumab + ipilimumab: increased lipase level, fatigue & diarrhoea

treatment-related deaths: 8 with nivolumab + ipilimumab, 4 with sunitinib

**C0002: Are the harms related to dosage or frequency of applying nivolumab?**

There is evidence from clinical trials that nivolumab monotherapy or nivolumab in combination with ipilimumab caused severe infusion reactions. In such cases, the infusion must be discontinued and patients must receive an appropriate alternative medical therapy. Patients who experienced a mild or moderate infusion reaction may receive nivolumab monotherapy or nivolumab plus ipilimumab with close monitoring and the use of premedication to prevent the occurrence of infusion reactions [2].

severe infusion reactions can occur

Of 547 nivolumab-plus-ipilimumab group patients, 58% and 27% had nivolumab and ipilimumab dose delays, respectively. Among sunitinib group patients (n = 535), dose delays were reported from 59% of patients and 53% of patients had dose reductions.

dose delays:
58% nivolumab
27% ipilimumab

**C0005: What are the susceptible patient groups that are more likely to be harmed through the use of nivolumab?**

There is no data available regarding the safety and efficacy of nivolumab in children younger than 18 years. Although there is no data available on the use of nivolumab during pregnancy, its use is not recommended since nivolumab has the potential to be transmitted from the mother to the foetus. Women at childbearing age should use effective contraception. There is no data available on whether nivolumab is secreted in human milk; moreover, the effect of nivolumab on male or female fertility is not known. In patients with moderate or severe hepatic impairment, nivolumab has to be administered with caution.

no data available on patients <18 years, pregnant or breastfeeding women, or on effect on fertility

*Table 2: CheckMate 214 trial: Treatment-related AEs occurring in ≥15% of treated patients in either group [18]*

| **Adverse event** (according to NCI CTCAE version 4.0) | **Intervention** (n = 547) | | **Control** (n = 535) | |
|---|---|---|---|---|
| | Any grade n (%) | Grade 3 or 4 n (%) | Any grade n (%) | Grade 3 or 4 n (%) |
| All events | 509 (93) | 250 (46) | 521 (97) | 335 (63) |
| Fatigue | 202 (37) | 23 (4) | 264 (49) | 49 (9) |
| Pruritus | 154 (28) | 3 (<1) | 49 (9) | 0 (0) |
| Diarrhoea | 145 (27) | 21 (4) | 278 (52) | 28 (5) |
| Rash | 118 (22) | 8 (1) | 67 (13) | 0 (0) |
| Nausea | 109 (20) | 8 (1) | 202 (38) | 6 (1) |
| Increased lipase level | 90 (16) | 56 (10) | 58 (11) | 35 (7) |
| Hypothyroidism | 85 (16) | 2 (<1) | 134 (25) | 1 (<1) |
| Decreased appetite | 75 (14) | 7 (1) | 133 (25) | 5 (<1) |
| Asthenia | 72 (13) | 8 (1) | 91 (17) | 12 (2) |
| Vomiting | 59 (11) | 4 (<1) | 110 (21) | 10 (2) |
| Anaemia | 34 (6) | 2 (<1) | 83 (16) | 24 (4) |
| Dysgeusia | 31 (6) | 0 (0) | 179 (33) | 1 (<1) |
| Stomatitis | 23 (4) | 0 (0) | 149 (28) | 14 (3) |
| Dyspepsia | 15 (3) | 0 (0) | 96 (18) | 0 (0) |
| Mucosal inflammation | 13 (2) | 0 (0) | 152 (28) | 14 (3) |
| Hypertension | 12 (2) | 4 (<1) | 216 (40) | 85 (16) |
| Palmar-plantar erythrodysesthesia | 5 (<1) | 0 (0) | 231 (43) | 49 (9) |
| Thrombocytopenia | 2 (<1) | 0 (0) | 95 (18) | 25 (5) |

*Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute, n = number*

## 7.3 Clinical effectiveness and safety – further studies

**no further phase II/III trials for untreated mRCC available**

There are no further phase II or phase III trials available evaluating the combination regimen of nivolumab plus ipilimumab for the first-line treatment of metastatic RCC.

**CheckMate 016: open-label phase I study**

**total of 5 treatment arms, patients of 3 arms received nivolumab + ipilimumab in different dosages**

**endpoints: safety, maximum tolerated dose and efficacy**

CheckMate 016 [19] is a phase I, open-label, multicentre, parallel-cohort, dose-escalation study assessing the efficacy and safety of nivolumab plus ipilimumab or nivolumab and a TKI in patients with mRCC. Patients who were eligible to receive nivolumab and ipilimumab were randomly assigned to receive either nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1, n = 47), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3, n = 47) or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3, n = 6). Eligible patients had histologically confirmed advanced RCC or mRCC with a clear-cell component, measurable disease according to RECIST 1.1 and a Karnofsky performance status of at least 80% at study enrolment. Patients of the initial cohorts (designed to gain safety information) of the N3I1 and N1I3 groups could either have received no prior treatment or had received

prior systemic therapy, whereas patients of the expansion cohorts (for safety and efficacy data) of the N3I1 , N1I3 and N3I3 groups were not allowed to have received prior systemic therapy for RCC.

N3I1 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg) patient characteristics

Patients of the N3I1 group had a median age of 53.0 years, and 91.5% of patients were male. According to the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification, 44.7% of patients had favourable risk, 48.9% of patients had intermediate risk and 6.4% of patients had poor risk. 97.9%, 31.9% and 46.8% of patients had prior surgery, prior radiotherapy and prior systemic therapy (most commonly with cytokines), respectively. More than half of patients (53.2%) did not receive any previous therapy; the most common treatment setting was metastatic (42.6%). The primary endpoint of the study was to evaluate overall safety and tolerability of the combination regimen nivolumab-plus-ipilimumab and to determine the maximum tolerated dose. Secondary endpoints were best overall response (BOR), ORR, DOR, time to response, PFS and 24-week PFS rate. Cut-off date of the CheckMate 016 trial was on 16 March 2016; the median follow-up was 22.3 months, minimum follow-up was 22 months. Patients of the N3I1 arm received a median of ten nivolumab doses, in patients of the N1I3 arm a median of seven nivolumab doses were administered.

high rates of AEs and SAEs, no treatment-related deaths

100% of patients of the N3I1 group and the N1I3 group experienced an AE of any grade. Among patients of the N3I1 arm, 91.5% of patients experienced a treatment-related AE of any grade (most frequent were fatigue, rash and pruritus) and 38.3% of patients had a treatment-related AE of grade 3 or 4. 95.7% of patients of the N1I3 arm had a treatment-related AE of any grade (most commonly fatigue, diarrhoea and pruritus) and 61.7% experienced a grade 3 or 4 treatment-related AE. 100% and 83.3% of patients of the N3I3 group reported an AE of any grade (fatigue and hypothyroidism were most frequent) and grade 3 or 4, respectively. Serious AEs (SAEs) occurred in 62.8% of patients of the N3I1 and N1I3 arms and 46.8% experienced a grade 3 or 4 SAE. 28.7% and 26.6% of patients of these two groups reported a treatment-related SAE of any grade and a treatment-related SAE of grade 3 or 4, respectively. There were no grade 5 treatment-related SAEs in either treatment group.

confirmed response in N3I1 and N1I3 arms: 40.4%

OS rate after 12 and 24 months higher in N1I3 arm

Due to the high censoring percentage, no efficacy results were presented for the N3I3 arm. In both the N3I1 and the N1I3 arm, the confirmed ORR was 40.4%. 10.6% of patients of the N3I1 arm achieved a complete response and 29.8% a partial response. In the N1I3 arm, no patient achieved a complete response, whereas 40.4% of patients had a partial response. In patients of the N3I1 arm, median OS was not reached; OS rate at 12 and 24 months was 81% and 67%, respectively. Patients of the N1I3 arm had a median OS of 32.6 months (95% CI, 26.0 months–not reached) and an OS rate at 12 and 24 months of 85% and 70%, respectively.

median PFS: 7.7 months in N3I1 group and 9.4 in N1I3 group

Among patients of the N3I1 group, median PFS was 7.7 months, PFS rates at 6, 12, 18 and 24 months were 55.6%, 40.0%, 28.9%, 18.7%. In the N1I3 arm, median PFS was 9.4 months and PFS rates at 6, 12, 18 and 24 months were 63.8%, 46.4%, 37.6% and not calculated, respectively.

# 8 Estimated costs

**A0021: What is the reimbursement status of nivolumab?**

4 mL = € 572.0
10 mL = € 1,430.0

Nivolumab (Opdivo®) is available as a concentrate for solution for infusion in vials of 4 mL (10 mg/mL) at € 572 and 10 mL (10 mg/mL) at € 1,430 (ex-factory prices) [29].

CheckMate 214: nivolumab 3 mg/kg, median treatment duration 7.9 months

Patients of the CheckMate 214 trial received 3 mg/kg IV of nivolumab every three weeks for four doses (induction phase), followed by 3 mg/kg IV of nivolumab every two weeks in the maintenance phase. Median treatment duration in the CheckMate 214 trial was 7.9 months in patients of the nivolumab-plus-ipilimumab group [18].

4 doses of nivolumab = € 13,728

Assuming an average body weight of 70 kg, 210 mg of nivolumab is needed for one dose of nivolumab treatment, costing € 3,432, resulting in costs of € 13,728 for the induction phase. Based on the median treatment duration of the CheckMate trial of 7.9 months comprising approximately 14 doses of nivolumab, treatment costs amount to € 48,048.

4 doses of ipilimumab = € 34,000

induction phase: € 47,728

maintenance phase: € 6,864 per month

Ipilimumab (Yervoy®) is available as a concentrate for solution for infusion in vials of 10 mL (5 mg/mL) at € 4,250 and 40 mL (5 mg/mL) at € 17,000 (ex-factory prices) [29]. In patients of the CheckMate 214 trial, ipilimumab was administered at a dose of 1 mg/kg every three weeks for four doses. Based on an average body weight of 70 kg, 70 mg of ipilimumab is needed for one infusion resulting in costs of about € 34,000 for four doses. Based on these calculations, total costs for the induction phase would be € 47,728. In total, for 7.9 months of nivolumab-plus-ipilimumab combination therapy (comprising induction phase followed by maintenance phase), costs of approximately € 82,048 would incur.

sunitinib: € 5,260 for one six-week cycle

Sunitinib (Sutent®) is available as 12.5 mg, 25 mg or 50 mg hard capsule with 30 tablets at € 1,315, € 2,660 or € 5,260 (ex-factory prices), respectively [29]. Patients of the CheckMate 214 trial received 50 mg of sunitinib orally once daily for four weeks of each six-week cycle, resulting in costs of € 5,260.0 for one cycle. Based on a median treatment duration of 7.8 months in CheckMate 214 trial patients, sunitinib treatment would cost approximately € 26,300.

# 9 Ongoing research

ongoing phase III trials

In June 2018, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase III trials, assessing the administration of nivolumab in patients with RCC, were identified:

- **NCT02231749:** CheckMate 214, the trial discussed in this assessment, is ongoing. The estimated study completion date is September 2019.

- **NCT03138512:** CheckMate 914 is a randomised trial comparing the combination of nivolumab and ipilimumab versus placebo in participants with localised RCC. The estimated study completion date is July 2023.
- **NCT03141177:** CheckMate 9ER is a randomised, open-label study assessing the combination of nivolumab with cabozantinib compared to sunitinib in previously untreated advanced or metastatic RCC. Estimated study completion date is April 2023.
- **NCT02940639** (study phase not available): NORA is a prospective study evaluating the real-life efficacy and safety of nivolumab in patients with advanced RCC after prior therapy. Estimated study completion date is October 2024.

**ongoing phase I and phase II trials**

Numerous phase I and phase II studies, assessing the efficacy and safety of nivolumab in patients with RCC were identified, including FRACTION-RCC (NCT02996110, a phase II study to test combination treatments), SUNIFORECAST (NCT03075423, a phase II randomised study of nivolumab plus ipilimumab versus standard of care in untreated and advanced non-clear-cell RCC) and BIONIKK (NCT02960906, a phase II BIOmarker-driven study with nivolumab and ipilimumab or vascular endothelial growth factor (VEGFR) TKI in patients with naïve metastatic kidney cancer). Furthermore, three phase IV trials (NCT02596035, NCT02982954 and NCT03444766), assessing the safety of nivolumab administration in advanced or metastatic RCC were found.

**phase IV safety trials**

# 10 Discussion

**nivolumab: approved in the US, not approved in Europe for the assessed indication**

Nivolumab (Opdivo®) is a human Ig4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor PD-1 with immune checkpoint inhibitory and antineoplastic activities [3]. To date, nivolumab has not been approved throughout Europe for the treatment of patients with advanced RCC who did not receive prior treatment [8]. Since April 2018, nivolumab in combination with ipilimumab has been approved in the US for the treatment of patients with intermediate- or poor-risk advanced RCC who did not receive prior therapy [9]. Sunitinib (Sutent®) is a multiple RTK inhibitor indicated for the treatment of advanced/metastatic RCC in adult patients [7]. Based on results of the CheckMate 214 trial, the EAU [17] strongly recommends to offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC.

**intermediate- and poor-risk patients: OS and ORR statistically significantly higher, OS: +15% at 18 months PFS: +3.2 months**

CheckMate 214, a randomised, open-label phase III study [18, 24], was conducted to assess the combination of nivolumab plus ipilimumab in patients with previously untreated advanced RCC. Sunitinib was chosen as comparator in this active controlled trial. After two formal interim analyses, intermediate- and poor-risk patients who received nivolumab plus ipilimumab showed a statistically significant benefit in OS and ORR as compared with sunitinib: the 12-month OS rate was 80% versus 72%, the 18-month OS rate was 75% versus 60%, with a HR for death of 0.63 (99.8% CI, 0.44–0.89; p <0.001) and an ORR of 42% versus 27% (p <0.001) in the respective groups. Since crossover has been permitted as noted below, no further valid OS data will be available. An evaluation of HRQoL in intermediate- and poor-risk patients showed better results in those who were treated with nivolumab plus ipilimumab than in patients who received sunitinib. According to Cella et al. [28], additional analyses are needed to clarify the clinical importance of HRQoL as a potential factor to influence survival.

**better HRQoL results with nivolumab + ipilimumab**

**median PFS prolonged with nivolumab + ipilimumab, difference not statistically significant**

Median PFS was prolonged in patients of the nivolumab-plus-ipilimumab group (11.6 months versus 8.4 months), whereas the between-group difference was not statistically significant. In patients of the ITT population, the OS benefit was also statistically significant with a HR for death of 0.68 (99.8% CI, 0.49–0.95; p <0.001). ORR and median PFS were higher with nivolumab plus ipilimumab in patients of the ITT population; however, the differences were not statistically significant. In the subgroup of favourable-risk patients, analyses of all endpoints favoured sunitinib.

**greater benefit in PD-L1 ≥1% patients**

**ORR was statistically significant in nivolumab-plus-ipilimumab patients with ≥1% PD-L1**

All patients who had quantifiable PD-L1 expression (including patients with less than 1% PD-L1 and 1% or greater PD-L1 expression) showed a prolonged OS when receiving nivolumab plus ipilimumab as compared to sunitinib. PFS also was prolonged among all patients with quantifiable PD-L1 expression receiving nivolumab plus ipilimumab compared to those receiving sunitinib (PD-L1 expression <1%: +0.6 months median PFS, PD-L1 expression ≥1%: +16.9 months median PFS); however, the gain was greater in patients who had 1% or greater PD-L1 expression: 22.8 months in nivolumab-plus-ipilimumab group patients versus 5.9 months in sunitinib group patients. The difference between the treatment groups with regard to ORR was statistically significant in patients with 1% or greater PD-L1 expression: 58% (nivolumab-plus-ipilimumab group) versus 22% (sunitinib group), p <0.001.

**age of the study population not representative of the European population**

In Germany, the median age of diagnosis of RCC is 67 years in men and 72 years in women [13]. Hence, the age of the study population was not representative of the actual patient population, particularly since the majority of study patients (265 of 425 in the nivolumab-plus-ipilimumab group and 259 of 422 in the sunitinib group) were younger than 65 years. CheckMate 214 subgroups including patients older than 65 years and older than 75 years were small, with wide CIs in OS analyses.

high rates of treatment-related AEs

higher discontinuation rate with nivolumab + ipilimumab

more deaths related to treatment with nivolumab + ipilimumab

Treatment-related AEs of any grade were reported in 93% of nivolumab-plus-ipilimumab group patients and in 97% of sunitinib group patients; treatment-related AEs of grade 3 or 4 occurred in 46% (nivolumab-plus-ipilimumab group) and 63% (sunitinib group) of patients. Treatment-related AEs leading to discontinuation of treatment were present in 22% of nivolumab-plus-ipilimumab group patients and in 12% of sunitinib group patients. Interestingly, although the rates of treatment-related AEs of any grade and of grade 3 or 4 were lower in patients receiving nivolumab plus ipilimumab, the rate of study treatment discontinuation due to treatment-related AEs was higher among patients who received nivolumab plus ipilimumab. In patients receiving nivolumab plus ipilimumab, eight treatment-related deaths occurred versus four treatment-related deaths among patients of the sunitinib group. Data regarding AEs were presented solely for the ITT population; however, AE data referring to intermediate- and poor-risk patients would have been of interest.

ESMO-MCBS
original: 4
adapted: 2

PFS was used to generate the ESMO-MCBS score, since there is no form available to assess ORR in randomised controlled trials and due to immature OS data. Given the non-curative setting of nivolumab, we applied form 2b of ESMO-MCBS in order to assess whether nivolumab satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of MCBS were applied [22, 23]. The application of ESMO-MCBS to the CheckMate 214 study resulted in a grade 4 in the original and a grade 2 in the adapted version of ESMO-MCBS (see Table 3). Therefore, nivolumab does demonstrate a meaningful clinical benefit; however, this only applies when the original scale is used. Differences in scores occur due to the use of the mean estimate of effect of the HR, which is to avoid a systematic bias in favouring drugs with a higher degree of uncertainty.

several methodological limitations:
high risk of bias

Both external and internal validity of the CheckMate 214 trial are compromised by several methodological limitations. The trial was conducted as an open-label study which may lead to a performance- and/or detection bias. Although pre-specified outcomes from the protocol, as well as withdrawal and reasons for discontinuations were reported, there is no AEs data of intermediate- and poor-risk patients available and there is a lack of CIs for PFS among the PD-L1 subgroups. Hence, due to the open-label setting, the unclear allocation concealment and additional aspects, a high risk of bias could be detected. Since the CheckMate 214 trial is ongoing until September 2019, final analysis is not completed. It should be noted that a protocol amendment (November 2017) permitted patients from the sunitinib group to cross over to the nivolumab-plus-ipilimumab group after the primary endpoint had been met.

nivolumab + ipilimumab:
considerably more expensive than sunitinib treatment

Assuming an average body weight of 70 kg, 210 mg of nivolumab is needed for one dose of nivolumab treatment, costing € 3,432 (ex-factory price [29]), resulting in costs of € 13,728 for the induction phase. Based on the median treatment duration in the CheckMate trial of 7.9 months comprising approximately 14 doses of nivolumab, treatment costs € 48,048. Additionally, four doses of ipilimumab are needed (1 mg/kg every 3 weeks); based on an average body weight of 70 kg, 70 mg of ipilimumab is needed for one infusion resulting in costs of € 34,000 for four doses. In total, costs of approximately € 82,048 for 7.9 months of combination therapy would incur. Median treatment duration with sunitinib was 7.8 months in CheckMate 214 trial patients with total costs of approximately € 26,300. Based on these calcula-

tions, the combination treatment of nivolumab plus ipilimumab is considerably more expensive than treatment with sunitinib.

**CheckMate 214: first phase III trial investigating front-line treatment with nivolumab + ipilimumab**

CheckMate 214 is the first phase III study investigating the efficacy and safety of the nivolumab-and-ipilimumab combination versus sunitinib in untreated patients with advanced RCC. There are results from a phase I study [19] indicating beneficial efficacy and safety results of nivolumab plus ipilimumab; however, evidence is limited due to a low sample size. Generally, evidence comparisons are difficult, since other studies investigating nivolumab plus ipilimumab were conducted in (partly heavily) pre-treated patients. The results of a currently ongoing (until 12/2021) phase III study (NCT02420821) evaluating the efficacy and safety of atezolizumab plus bevacizumab versus sunitinib in untreated patients with inoperable, locally advanced or metastatic RCC may be useful to identify the role of monoclonal antibodies in this treatment setting. More data is needed to determine the most effective, safest and most appropriate treatment regimen for untreated patients with advanced RCC.

**role of monoclonal antibodies**

**CheckMate 214 proves clinical benefit, but more evidence is required**

CheckMate 214 study results show that the combination of nivolumab and ipilimumab provides clinical benefit in previously untreated, intermediate- and poor-risk patients. However, the high rate of treatment-related AEs has to be considered. Moreover, data regarding AEs for intermediate- and poor-risk patients and, additionally, long-term efficacy and safety data of the combination therapy would be of interest. Also, it may be preferable to clarify the role of monoclonal antibodies such as atezolizumab or pembrolizumab in this therapeutic setting. Since CheckMate 214 is the only phase III trial providing results of nivolumab plus ipilimumab in untreated patients with advanced RCC, more data is needed to evaluate this combination

*Table 3: Benefit assessment based on ESMO-MCBS v1.1 and an adapted version of ESMO-MCBS [22, 23]*

| ESMO-MCBS | Subgroup | Active substance | Indication | Intention | PE | Form | MG standard treatment | Efficacy | | | | Safety | | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *MG months* | *HR (95% CI)* | *Score calculation* | *PM* | *Toxicity* | *QoL* | | |
| **Adapt-ed ESMO-MCBS** | Intermediate- and poor-risk patients | Nivolumab | Advanced RCC (1st line) | NC | OS & ORR* | 2b[2] | >6 months | +3.2 | 0.82 (0.64–1.05) | HR >0.65 | 1 | -17% grade 3–4 AEs[3], +10% discontinuation | Improved HRQoL | +1 [4] | **2** |
| **Original ESMO-MCBS** | Intermediate- and poor-risk patients | Nivolumab | Advanced RCC (1st line) | NC | OS & ORR* | 2b[2] | >6 months | +3.2 | 0.82 (0.64–1.05) | HR ≤0.65 AND gain ≥3 months | 3 | x | Improved HRQoL | +1 [4] | **4** |

*Abbreviations: AEs = adverse events, AJ = adjustments, CI = confidence interval, ESMO = European Society for Medical Oncology, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, HRQoL = health-related quality of life, MCBS = Magnitude of Clinical Benefit Scale, MG = median gain, NC = non-curative setting, ORR = objective response rate, OS = overall survival, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life, RCC = renal cell carcinoma, * co-primary endpoints*

**DISCLAIMER**

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[2] PFS was used to generate the ESMO-MCBS score, as there is no form available to assess ORR in randomised controlled trials and OS was not mature at the time of analysis

[3] Data is based on the intention-to-treat population, since there are no separate results for this subgroup available

[4] Upgrade due to an improvement in HRQoL

# 11 References


[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals.Version 3.0. 2013 [cited 2015-10-30]. Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] European Medicines Agency. EPAR - Product Information.Opdivo. [2018-06-26]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf.

[3] National Cancer Institute. NCI Drug Dictionary. Nivolumab. [cited 2018-06-28]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/nivolumab.

[4] U.S. Food and Drug Administration. Drugs@FDA. Label Information. Opdivo. [cited 2018-06-26]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf.

[5] European Medicines Agency. EPAR - Product Information. Yervoy. [cited 2018-07-31]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf.

[6] U.S. Food and Drug Administration. Drugs@FDA.Label information.Yervoy. [cited 2018-07-31].

[7] European Medicines Agency. EPAR - Product Information. Sutent. [2018-06-26]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000687/WC500057737.pdf.

[8] European Medicines Agency. Opdivo. [2018-06-29]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003985/human_med_001876.jsp&mid=WC0b01ac058001d124.

[9] U.S. Food and Drug Administration. Drugs@FDA. Opdivo. [2018-06-29]; Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125554.

[10] Atkins MB. Epidemiology, pathology, and pathogenesis of renal cell carcinoma. In: Richie JP, editors. UpToDate. Waltham, MA. (cited 2018-06-29): UpToDate; 2018.

[11] Atkins MB. Clinical manifestations, evaluation, and staging of renal cell carcinoma. In: Richie JP, editors. UpToDate. Waltham, MA (cited 2018-06-29): UpToDate; 2018.

[12] Statistik Austria. Krebserkrankungen - Niere. [2018-07-01]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/niere/index.html.

[13] Zentrum für Krebsregisterdaten. Krebsarten.Nierenkrebs. [2918-07-01]; Available from: https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Nierenkrebs/nierenkrebs_node.html.

[14] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. [2018-07-24]; Available from: https://seer.cancer.gov/statfacts/html/kidrp.html.

[15] Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27 (Supplement 5): v58–v68, 2016.

[16] National Comprehensive Cancer Network® (NCCN). NCCN Guidelines Version 4.2018. Kidney Cancer. [2018-06-29]; Available from: www.nccn.org.

[17] Powles T, Albiges L, Staehler M, Bensalah K, Dabestani S, Giles RH, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. European urology. 2017.

[18] Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-90.

[19] Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol 35:3851-3858.

[20] EUnetHTA - European Network for Health Technology Assessment. Internal validity of randomised controlled trials 2013, adapted version (2015). Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

[21] EUnetHTA Guidelines. Levels of evidence. Applicability of evidence for the context of a relative effectiveness assessment of pharmaceuticals. February 2013, adapted version (2015). Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Levels-of-Evidence-Applicability-of-evidence-for-the-context-of-a-relative-effectiveness-assessment_Amended-JA1-Guideline_Final-Nov-2015.pdf.

[22] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology. 2015; 26(8):1547-73).

[23] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K, et al. Utilisation of the ESMO-MCBS in practice of HTA. Annals of Oncology 2016;27(11):2134-6.

[24] Supplement to: Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90

[25] Protocol for: Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.

[26] Roy J, Daniels MJ. A General Class of Pattern Mixture Models for Nonignorable Dropout with Many Possible Dropout Times. Biometrics 2008 Jun; 64(2): 538–545

[27] NCSS Statistical Software. Mixed Models – Repeated Measures. [cited 2018-07-31]; Available from: https://ncss-wpengine.netdna-ssl.com/wp-content/themes/ncss/pdf/Procedures/NCSS/Mixed_Models-Repeated_Measures.pdf.

[28] Cella D, Grünwald V, Escudier B, Hammers H, George S, Nathan P, et al. Quality of Life in Patients With Advanced Renal Cell Carcinoma in the Randomized, Open-Label CheckMate 214 Trial. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2018; June 1–5, 2018; Chicago, IL, USA.

[29] Warenverzeichnis Apothekerverlag Online. [2018-07-04]; Available from: http://warenverzeichnis.apoverlag.at.

# 12 Appendix

*Table 4: Administration and dosing of nivolumab (Opdivo®) [2, 7]*

| | Technology | Comparator |
|---|---|---|
| **Administration mode** | Intravenous infusion (IV) | Oral administration |
| **Description of packaging** | Opdivo® is available as a concentrate for solution for infusion.<br>4 mL of concentrate in a 10-mL vial (Type 1 glass) with a stopper (coated butyl rubber) and a dark blue flip-off seal (aluminium). Pack size of 1 vial.<br>10 mL of concentrate in a 10 mL vial (Type 1 glass) with a stopper (coated butyl rubber) and a grey flip-off seal (aluminium). Pack size of 1 vial.<br>Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. | Sutent® 12.5 mg hard capsules (gelatin capsules with orange cap and orange body, printed with white ink "Pfizer" on the cap, "STN 12.5 mg" on the body, and containing yellow to orange granules)<br>Sutent® 25 mg hard capsules (gelatin capsules with caramel cap and orange body, printed with white ink "Pfizer" on the cap, "STN 25 mg" on the body, and containing yellow to orange granules)<br>Sutent® 37.5 mg hard capsules (gelatin capsules with yellow cap and yellow body, printed with black ink "Pfizer" on the cap, "STN 37.5 mg" on the body, and containing yellow to orange granules)<br>Sutent® 50 mg hard capsules (gelatin capsules with caramel cap and caramel body, printed with white ink "Pfizer" on the cap, "STN 50 mg" on the body, and containing yellow to orange granules) |
| **Total volume contained in packaging for sale** | Opdivo® 10 mg/mL concentrate for solution for infusion<br>One vial of 4 mL contains 40 mg of nivolumab.<br>One vial of 10 mL contains 100 mg of nivolumab. | 12.5 mg hard capsules<br>25 mg hard capsules<br>37.5 mg hard capsules<br>50 mg hard capsules |
| **Dosing** | CheckMate 214 trial: Nivolumab and ipilimumab were administered IV at a dose of 3 mg/kg over 60 minutes and 1 mg/kg over 30 minutes, respectively, every 3 weeks for 4 doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg/kg every 2 weeks (maintenance phase). | CheckMate 214 trial: Sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of each 6-week cycle. |
| **Median treatment duration** | CheckMate 214 trial: Median treatment duration was 7.9 months in patients receiving nivolumab plus ipilimumab | CheckMate 214 trial: Median treatment duration was 7.8 months in patients receiving sunitinib. |
| **Contraindications** | Hypersensitivity to the active substance or to any of the excipients (sodium citrate dehydrate, sodium chloride, mannitol (E421), pentetic acid (diethylenetriaminepenta-acetic acid), polysorbate 80, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections) | Hypersensitivity to the active substance or to any of the excipients (for detailed list, see product information) |
| **Drug interactions** | Nivolumab is a human monoclonal antibody; as such, pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug-metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.<br>The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab administration, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab therapy to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude response to nivolumab. | In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] $C_{max}$ and AUC $_{0-\infty}$ values of 49% and 51%, respectively.<br>Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.<br>Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dose of Sutent® may need to be reduced to a minimum of 37.5 mg daily for GIST and mRCC or 25 mg daily for pNET, based on careful monitoring of tolerability. |

| | | |
|---|---|---|
| | | Limited clinical data are available on the interaction between sunitinib and BCRP inhibitors, and the possibility of an interaction between sunitinib and other BCRP inhibitors cannot be excluded.<br><br>In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite]<br>$C_{max}$ and $AUC_{0-\infty}$ values of 23% and 46%, respectively.<br><br>Administration of sunitinib with potent CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort/Hypericum perforatum) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered. If this is not possible, the dose of Sutent® may need to be increased in 12.5 mg increments (up to 87.5 mg per day for GIST and mRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability. |

*Abbreviations: AUC = area under the curve, BCRP = breast cancer resistance protein, $C_{max}$ = maximum concentration, GIST = gastrointestinal stromal tumour, IV = intravenous, mRCC = advanced/metastatic renal cell carcinoma, pNET = pancreatic neuroendocrine tumour*

*Table 5: Characteristics of the CheckMate 214 trial*

| | | | |
|---|---|---|---|
| **Title:** Nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma [18, 24, 25] | | | |
| **Study identifier** | NCT02231749, EudraCT number: 2014-001750-42, CA209-214, CheckMate 214 | | |
| **Design** | Randomised, open-label phase III trial | | |
| | Duration of main phase: | | Patients were randomly assigned to treatment from October 2014 through February 2016.<br>CheckMate 214 trial is ongoing until September, 2019.<br>Median follow-up: 25.2 months<br>Minimum follow-up: 17.5 months |
| **Hypothesis** | Superiority: Treatment with nivolumab combined with ipilimumab will improve PFS, OS or both compared to sunitinib monotherapy in patients with previously untreated mRCC. | | |
| **Funding** | Bristol Myers Squibb and Ono Pharmaceutical | | |
| **Treatment groups (ITT population)** | Intervention (n = 547) | | Induction phase: patients received nivolumab (3 mg/kg over a period of 60 minutes) and ipilimumab (1 mg/kg over a period of 30 minutes) IV, every 3 weeks for four doses.<br>Maintenance phase: patients received nivolumab monotherapy (3 mg/kg) every two weeks. |
| | Control (n = 535) | | Patients received sunitinib at a dose of 50 mg orally once daily for four weeks of each 6-week-cycle. |
| **Endpoints and definitions** | Objective response rate in intermediate- and poor-risk patients (co-primary endpoint) | ORR | ORR was defined as the percentage of patients having a confirmed best response of complete response or partial response according to RECIST, version 1.1, on the basis of assessment by an independent radiology review committee. |
| | Progression-free survival in intermediate- and poor-risk patients (co-primary endpoint) | PFS | PFS was defined as the time from randomisation to first RECIST-defined progression or death. |
| | Overall survival in intermediate- and poor-risk patients (co-primary endpoint) | OS | OS was defined as the time from randomisation to death. |
| | ORR, PFS and OS in the ITT population (secondary endpoints) | ORR, PFS, OS | See above. |
| | ORR, PFS and OS in favourable-risk patients (exploratory endpoints) | ORR, PFS, OS | See above. |
| | Level of tumour PD-L1 level expression survival in intermediate- and poor-risk patients (additional exploratory endpoint) | PD-L1 level | This endpoint included outcomes according to the level of tumour PD-L1 expression (≥1% vs. <1%) as assessed at a central laboratory with the use of the Dako PD-L1 IHC 28-8 pharmDx test. |
| | Health-related quality of life in intermediate- and poor-risk patients (additional exploratory endpoint) | HRQoL | HRQoL was assessed on the basis of the score on the NCCN/FACT-Kidney Symptom Index (FKSI-19). |
| **Database lock** | 7 August 2017 | | |
| **Results and analysis** | | | |

<table>
<tr><td colspan="4">Title: Nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma [18, 24, 25]</td></tr>
<tr><td>Study identifier</td><td colspan="3">NCT02231749, EudraCT number: 2014-001750-42, CA209-214, CheckMate 214</td></tr>
<tr><td>Analysis description</td><td colspan="3">It was estimated that 1,070 patients would undergo randomisation, with 820 having IMDC intermediate or poor risk (the proportion expected according to the distribution in the general population and the number needed for robust statistical analyses). Enrolment was discontinued once approx. 820 patients (77%) with IMDC intermediate or poor risk had undergone randomisation. The overall alpha level was 0.05, split among three co-primary endpoints. ORR was analysed at an alpha level of 0.001. PFS was evaluated at an alpha level of 0.009, with a power of 80% or more. OS was evaluated at an alpha level of 0.04 with 90% power (independent of co-primary endpoints) on the basis of a HR of 0.77, accounting for two formal interim analyses after 51% and 75% of deaths had occurred, using a stratified log-rank test. An O'Brien and Fleming alpha spending function was used to determine nominal significance levels that were based on the number of deaths for the interim and final analyses and stopping boundaries, and an adjusted alpha level of 0.002 was used for the first interim analysis. Critical HR for the first interim analysis of OS was 0.72. Stratified HR between treatment groups is presented along with the 99.8% confidence interval (adjusted for interim analyses). For PFS, a two-sided stratified 99.1% CI for the HR was calculated. CIs were defined on the basis of the respective alpha level allocated to that endpoint. Estimates of response rate, along with the exact two-sided 95% CI by the Clopper-Pearson method were computed. OS, PFS, and duration of response were estimated with the use of Kaplan-Meier methods. For QoL assessments, descriptive statistics and change from baseline were conducted for the FKSI-19 score. Calculations of p-values to evaluate the between-group difference in mean change from baseline were based on an independent-samples t-test under the assumption that variances were unequal. Both a pattern-mixture model and a restricted maximum likelihood-based repeated-measures approach were used to confirm descriptive data.</td></tr>
<tr><td rowspan="11">Analysis population</td><td>Inclusion</td><td colspan="2">❁ Patients aged 18 years or older<br>❁ Previously untreated advanced RCC with a clear-cell component<br>❁ Measureable disease according to RECIST (version 1.1)<br>❁ Karnofsky performance status score of at least 70 (on a scale from 0 to 100, with lower scores indicating greater disability)</td></tr>
<tr><td>Exclusion</td><td colspan="2">❁ CNS metastases<br>❁ Autoimmune disease<br>❁ Use of glucocorticoids or immunosuppressants</td></tr>
<tr><td>Characteristics of IMDC intermediate- and poor-risk patients</td><td>Intervention (n = 425)</td><td>Control (n = 422)</td></tr>
<tr><td>Median age (range), years</td><td>62 (26–85)</td><td>61 (21–85)</td></tr>
<tr><td>Male, n (%)<br>Female, n (%)</td><td>314 (74)<br>111 (26)</td><td>301 (71)<br>121 (29)</td></tr>
<tr><td>IMDC prognostic risk, n (%)<br>Favourable<br>Intermediate<br>Poor</td><td><br>0<br>334 (79)<br>91 (21)</td><td><br>0<br>333 (79)<br>89 (21)</td></tr>
<tr><td>Geographic region, n (%)<br>United States<br>Canada and Europe<br>Rest of the world</td><td><br>112 (26)<br>148 (35)<br>165 (39)</td><td><br>111 (26)<br>146 (35)<br>165 (39)</td></tr>
<tr><td>Quantifiable tumour PD-L1 expression, n/total n with evaluable data (%)<br><1%<br>≥1%</td><td><br>284/384 (74)<br>100/384 (26)</td><td><br>278/392 (71)<br>114/392 (29)</td></tr>
<tr><td>Previous radiotherapy, n (%)</td><td>52 (12)</td><td>52 (12)</td></tr>
<tr><td>Previous nephrectomy, n (%)</td><td>341 (80)</td><td>319 (76)</td></tr>
<tr><td>Number of sites with target or nontarget lesions, n (%)<br>1<br>≥2</td><td><br>90 (21)<br>335 (79)</td><td><br>84 (20)<br>337 (80)</td></tr>
<tr><td>Most common sites of metastasis, n (%)<br>Lung<br>Lymph node<br>Bone<br>Liver</td><td><br>294 (69)<br>190 (45)<br>95 (22)<br>88 (21)</td><td><br>296 (70)<br>216 (51)<br>97 (23)<br>89 (21)</td></tr>
<tr><td colspan="4">Applicability of evidence</td></tr>
<tr><td>Population</td><td colspan="3">The CheckMate 214 trial included patients with previously untreated advanced RCC with a clear-cell component. The majority of ITT-population patients had IMDC intermediate or poor risk.</td></tr>
</table>

| **Title:** Nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma [18, 24, 25] | |
|---|---|
| **Study identifier** | NCT02231749, EudraCT number: 2014-001750-42, CA209-214, CheckMate 214 |
| Intervention | Participants of the CheckMate 214 trial received nivolumab 3 mg/kg over 60 minutes and ipilimumab 1mg/kg over 30 minutes every 3 weeks for 4 doses (induction phase), followed by nivolumab monotherapy 3 mg/kg every 2 weeks (maintenance phase). Except for the infusion rate, this dosing schedule is equal to the recommended dosage schedule approved by the FDA. |
| Comparator | Sunitinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) which is indicated for the treatment of advanced/metastatic RCC in adult patients. |
| Outcomes | In intermediate- and poor-risk patients treated with nivolumab plus ipilimumab, OS and ORR rates were significantly higher than in patients treated with sunitinib. Patients reported better HRQoL with nivolumab plus ipilimumab than with sunitinib. Patients generally had high rates of treatment-related AEs of any grade in either group, treatment-relates AEs of grade 3 or 4 were higher among patients receiving sunitinib. However, the rate of discontinuation due to treatment-related AEs was higher in patients who received nivolumab plus ipilimumab. |
| Setting | The CheckMate 214 trial is an international study with 26% of the participants (IMDC intermediate- and poor-risk patients) from the United States, 35% from Canada and Europe and 39% of patients from the rest of the world. |

*Abbreviations: CI = confidence interval, CNS = central nervous system, FACT = Functional Assessment of Cancer Therapy, FKSI = Functional Assessment of Cancer Therapy-Kidney Symptom Index, HR = hazard ratio, HRQoL = health-related quality of life, IHC = immunohistochemistry, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, ITT = intention to treat, IV = intravenous, mRCC = metastatic renal cell carcinoma, n = number, NCCN = National Comprehensive Cancer Network, ORR = objective response rate, OS = overall survival, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, RCC = renal cell carcinoma, RECIST = Response Evaluation Criteria in Solid Tumors , QoL = quality of life*

*Table 6: Risk of bias assessment on study level is based on EUnetHTA (internal validity of randomised controlled trials) [20]*

| Criteria for judging risk of bias | | Risk of bias |
|---|---|---|
| **Adequate generation of randomisation sequence:** Patients were enrolled in the study by calling an IVRS to obtain the subject number. 1:1 randomisation was performed with a block size of 4 with stratification according to IMDC risk score (0 vs. 1 or 2 vs. 3 to 6) and geographic region (US vs. Canada and Europe vs. the rest of the world) | | Yes |
| **Adequate allocation concealment** | | Unclear |
| **Blinding:** | **Patient:** open-label | No |
| | **Treating physician:** open-label | No |
| **Selective outcome reporting unlikely:** Pre-specified outcomes from the protocol were reported; withdrawals and reasons for discontinuations were reported. However, there is no AEs data reported from intermediate- and poor-risk patients and there is a lack of CIs for PFS among the PD-L1 subgroups. | | No |
| **No other aspects which increase the risk of bias:** The study was funded by Bristol-Myers Squibb and Ono Pharmaceutical. Nivolumab, ipilimumab and sunitinib were provided by the sponsors (except when sunitinib was procured as a local commercial product in certain countries). The trial was designed by the authors in collaboration with the sponsors. Bristol-Myers Squibb collected and analysed the data with the authors. Medical writing support was funded by Bristol-Myers Squibb. | | No |
| **Risk of bias – study level** | | High |

*Abbreviations: AEs = adverse events, CIs = confidence intervals, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IVRS = interactive voice response system, PD-L1 = programmed death-ligand 1, PFS = progression-free survival*