CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Clinical Guidance Report

# Nivolumab (Opdivo) plus Ipilimumab (Yervoy) for Advanced Renal Cell Carcinoma

November 1, 2018

# DISCLAIMER

**Not a Substitute for Professional Advice**

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

**Liability**

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

**FUNDING**

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

## INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

# TABLE OF CONTENTS

# 1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma (RCC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma (RCC) conducted by the genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma (RCC), a summary of submitted Provincial Advisory Group Input on nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma (RCC), and a summary of submitted Registered Clinician Input on nivolumab (Opdivo) plus ipilimumab (Yervoy) for advanced renal cell carcinoma (RCC), and are provided in Sections 2, 3, 4, and 5 respectively.

## 1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of nivolumab (Opdivo) plus ipilimumab (Yervoy) for the treatment of patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

The Health Canada regulatory approval was for the use of nivolumab is indicated in combination with ipilimumab, for the treatment of intermediate/poor risk advanced RCC patients. Both agents in the combination treatment are given intravenously. The recommended dose for nivolumab is 3 mg/kg IV every 3 weeks for 4 doses when combined with ipilimumab and 3mg/kg every 2 weeks when given as a monotherapy. The recommended dose for ipilimumab is 1 mg/kg IV every 3 weeks for 4 doses. Patients in the CheckMate 214 trial could continue to receive treatment beyond RECIST defined disease progression.

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One pivotal clinical trial was identified that met the eligibility criteria and is included in this systematic review (Please see Table 4). CheckMate 214[2] is a phase III, randomized, multicentre open-label study assessing the efficacy and safety of the combination of nivolumab + ipilimumab vs. sunitinib monotherapy in the treatment of adult (≥ 18 years) subjects with previously untreated, advanced or metastatic RCC.

Between October 2014 and February 2016, 1096 eligible adult patients with previously untreated advanced or metastatic RCC patients were randomized, and of those 1082 received treatment. The study included adults (>18 years) with advanced (either not amenable to curative surgery or radiation, or AJCC Stage IV) histologically confirmed RCC with a clear-cell component. Prior systemic therapy for RCC was not permitted except for one prior adjuvant or neoadjuvant therapy provided such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. Subjects were to have a Karnofsky Performance Status (KPS) of at least 70%. To be eligible for the intermediate/poor-risk cohort, at least 1 of the 6 following prognostic factors as per IMDC criteria had to be present: 1) KPS equal to 70%; 2) less than a year from diagnosis to randomization; 3) hemoglobin < lower limit of normal; 4) corrected calcium concentration > 10 mg/dL; 5) absolute neutrophil count > upper limit of normal; 6) platelet count > ULN.

Participants in the two study arms were well-balanced with respect to demographic characteristics. The vast majority (>71%) of patients were male and there was an overall median age of 61-62 years in both treatment groups. A total of 79% patients had a prognostic score of 1–2 (intermediate-risk) while the remaining 21% were within the poor-risk category. Approximately a quarter of all patients were enrolled from the United States, with approximately 35% enrolled from Canada or Europe and 39% enrolled from other parts of the world. Greater than 75% of all patients had previous nephrectomy, but less than 13% of all patients had previous radiotherapy. Metastases most often occurred in the lungs, followed by lymph node, bones and liver.

The co-primary end points were the objective response rate, progression-free survival, and overall survival among intermediate- and poor-risk patients. Secondary end points included the objective response rate, progression-free survival, and overall survival, all in the intention-to-treat population; and the incidence rate of adverse events among all treated patients. Key exploratory endpoints included health-related quality of life on the basis of the score on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19), both in intermediate- and poor-risk patients.

Patients in both groups were allowed to continue therapy after initial investigator-assessed, RECIST-defined progression if they had clinical benefit without disabling toxic effects. A total of 28.5% (157/550) of treated subjects in the nivolumab + ipilimumab group and 23.6% (129/546) of treated subjects in the sunitinib group were treated beyond progression (defined as a last dosing date after investigator-assessed RECIST v1.1 progression date). Patients discontinued trial therapy on evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions) according to investigator assessment.

The sample size of the study accounted for the three co-primary efficacy end points: ORR and PFS as per Independent Radiology Review Committee (IRRC), and OS evaluated in intermediate and poor-risk subjects with previously untreated mRCC. The overall alpha for this study was 0.05, which was split into 0.001 for ORR, 0.009 for PFS, and 0.04 for OS. This study was powered to approximately 80% for PFS analysis and 90% for OS analysis, to determine statistically significant differences between treatment arms. Overall survival was evaluated on the basis of a hazard ratio of 0.77, accounting for two formal interim

analyses after 51% and 75% of deaths had occurred, using a stratified log-rank test. It was estimated that 1070 patients would undergo randomization, 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). Enrollment was discontinued once approximately 820 patients (77%) with IMDC intermediate or poor risk had undergone randomization.

Overall, CheckMate 214 was a well-designed phase III RCT. However, the trial used an open-label design, making the investigators, other study personnel and participants aware of the treatment allocation (Table 5). The rationale for an open-label methodology was based on multiple factors, including different routes of administration (intravenous for nivolumab plus ipilimumab versus oral for sunitinib), different treatment schedules (every three weeks for four doses for nivolumab plus ipilimumab, then nivolumab every 2 weeks versus daily for 4 weeks for sunitinib), different dose modification rules, different safety profiles and different management of AEs between the two study groups. Although the primary endpoints of the study, OS, ORR, and PFS are objective outcomes or objectively assessed, an open-label study design could have introduced some levels of bias to the investigator's assessment of PFS and ORR, patient-reported outcomes, as well as assessment and reporting of drug-related AEs. Furthermore, assessment of HRQoL outcomes were exploratory and the clinical significance of the results remain uncertain.

**RESULTS:**

**CO-PRIMARY OUTCOMES**

After the August 2017 cut-off, the independent Data Monitoring Committee (DMC) recommended stopping the trial at the first interim analysis on September 6th, 2017 for reasons of statistical superiority.

**Overall Survival (OS) in IMDC Intermediate/Poor-Risk Subjects**

Nivolumab plus ipilimumab had a significant overall survival benefit compared to sunitinib; the 12-month overall survival rate was 80% (95% CI, 76 to 84) with nivolumab plus ipilimumab versus 72% (95% CI, 67 to 76) with sunitinib, and the 18-month overall survival rate was 75% (95% CI, 70 to 78) versus 60% (95% CI, 55 to 65) The between-group difference met the prespecified threshold for statistical significance at an adjusted alpha level of 0.002 for first interim analysis (hazard ratio for death, 0.63; 99.8% CI, 0.44 to 0.89; P<0.001) (Table 8). The median overall survival was not reached (95% CI, 28.2 months to not estimable) with nivolumab plus ipilimumab versus 26.0 months (95% CI, 22.1 to not estimable) with sunitinib. Nivolumab + ipilimumab provides a statistically significant OS gain over sunitinib and a 37% reduction in the risk of death in patients with previously untreated advanced or metastatic RCC in the intermediate/poor-risk group.

**Progression-Free Survival (PFS) per IRRC in IMDC Intermediate/Poor-Risk Subjects**
The interim analysis showed that the median PFS was 11.6 months (95% CI, 8.7 to 15.5) for nivolumab + ipilimumab, compared with 8.4 months (95% CI, 7.0 to 10.8 for sunitinib (Table 8). The between-group difference did not meet the prespecified threshold (P = 0.009) for statistical significance (hazard ratio for disease progression or death, 0.82; 99.1% CI, 0.64

to 1.05; P = 0.03). Although not statistically significant, median PFS with nivolumab + ipilimumab was more than 3 months longer than with sunitinib.

The Kaplan-Meier curves, presented as Figure 2 in Motzer et al,[2] overlapped until approximately six months and then separated, favouring nivolumab + ipilimumab beyond this time point; the effect was more pronounced over time when looking at the tail of the curve.

**Objective Response Rate (ORR) in IMDC Intermediate/Poor-Risk Subjects**
The combination of nivolumab + ipilimumab was associated with a significantly higher ORR than sunitinib, as assessed by IRRC, with 42% (95% CI, 37 to 47) of patients achieving ORR criteria in the nivolumab + ipilimumab group vs. 27% in the sunitinib group (95% CI, 22 to 31; *P*< 0.001; Table 8). A significantly higher proportion of subjects achieved a CR in the nivolumab + ipilimumab group compared to the sunitinib group (9% vs. 1%, respectively, *P*< 0.001).

**Secondary Endpoints**

**Duration of Response**
The interim analysis of the CheckMate 214[2] data showed a trend towards an increased DOR in patients who received nivolumab + ipilimumab. The median DOR was not reached, however the minimum DOR was 21.8 months for patients treated with nivolumab + ipilimumab, whereas those treated with sunitinib demonstrated a median duration of response of 18.2 months (Table 8).

**Time to Response and Duration of Response per IRRC**
In intermediate/poor-risk subjects, responses in the nivolumab + ipilimumab group occurred early (median TTR of 2.8 months) and were durable (median DOR was not reached at the time of database lock, 95% CI 21.8-NE). In the sunitinib group, median time to response was similar (3.0 months, 95% CI 0.6-15.0) but responses were less durable (median DOR 18.2 months, 95% CI 14.8-NR).

***Health-related Quality of Life***
The exploratory outcome of patient-reported disease related symptoms was assessed using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19) in intermediate- and poor-risk patients. FKSI-19 scores range from 0 to 76, with higher scores indicating fewer symptoms.[2] Patients' general health-related quality of life (HRQoL) was assessed using the EuroQol EQ-5D and the Functional Assessment of Cancer Therapy-General (FACT-G).[4]

With completion rates of the FKSI-19 questionnaire exceeding 80% during the first 6 months, the nivolumab + ipilimumab group reported numerically higher scores compared to baseline scores and versus the sunitinib group for all assessments during the first 6 months ($p<0.001$)[2] and were sustained at all but two post-baseline time points through two years of follow-up ($p<0.05$) (Figure 3A).[4] The mean change from baseline in FACT-G total score was significantly improved compared with sunitinib at approximately half of the assessment time points (Figure 3B).[3] Mean EQ-5D VAS scores increased over time with both nivolumab + ipilimumab and sunitinib; differences between treatment arms were not statistically significant (Figure 3C).[3]

Time to deterioration (TTD) in FKSI-19 total score (defined as the first decrease of ≥3 points) was significantly delayed with nivolumab + ipilimumab versus sunitinib (HR 0.54; 95% CI, 0.46–0.63; *P* < 0.0001) with a median TTD of 2.2 months versus 1.0 months for nivolumab + ipilimumab versus sunitinib.[3] TTD was also significantly delayed with nivolumab + ipilimumab versus sunitinib in both FACT-G total (HR 0.63; 95% CI, 0.52–0.75; *P* < 0.0001) and EQ-5D VAS (HR 0.75; 95% CI, 0.63–0.89; *P* = 0.0016) scores, both defined as the first decrease of ≥7 points.[3]

Mixed effect model repeat measurement (MMRM) analysis of the FKSI-19 for the difference between nivolumab + ipilimumab group compared to the sunitinib group in total was 2.63 (95% CI 1.13-4.13) (p<0.05). For disease-related symptoms, the difference was 0.75 (0.10-1.40) and for physical disease related symptoms the difference observed was 1.19 (0.28-2.11) (p<0.05 for both). Differences were also significant in favor of nivolumab + ipilimumab for the EQ-5D utility index and VAS scores.[3]

[redacted]

(*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed*.). In fact, across all 3 patient-reported scales, the nivolumab + ipilimumab group reported numerically higher scores compared to baseline scores and compared to the sunitinib group, explicitly implying a favorable outcome.[8]

**Harms Outcomes**

**Treatment-Related Adverse Events**

Safety analyses were conducted in all 1082 treated subjects who received at least 1 dose of study drug. The all-treated population was the primary population for safety analyses to maximize the size of the safety database. Safety analyses for the intermediate/poor risk population were consistent with the all treated population. In the all-treated population, 93% and 97% of subjects reported at least one treatment-related AE in the nivolumab + ipilimumab and sunitinib groups, respectively (Table 9).[2] The proportion of all causality grade ≥3 AE's was lower in the nivolumab + ipilimumab group (46%) compared to the sunitinib group (63%).[5]

The most common AEs (any grade) in the nivolumab + ipilimumab group were fatigue (37%), pruritus (28%) and diarrhea (27%), whereas in the sunitinib group the most common events were diarrhea (52%), fatigue (49%) and palmar-plantar erythrodysesthesia syndrome (43%). Reporting of hypertension was 40% in the sunitinib group (16% with grade 3 or 4) compared to 2% (<1% with grade 3 or 4) in the nivolumab + ipilimumab group.[2]

Any-grade treatment-related select AEs resolved in 72-92% of patients receiving nivolumab + ipilimumab and in 67-100% of patients receiving sunitinib, with the exception of 43% and 37% of endocrinopathies, respectively, which required permanent hormone replacement.[5] Of the 436 patients treated with nivolumab plus ipilimumab who had immune-mediated adverse events that included skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories, 152 (35%) received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent). Concomitant immune-modulating medications (IMMs) were administered

for management of AEs in 72% of patients in the nivolumab plus ipilimumab arm and 33% of patients in the sunitinib arm.[5] IMM included systemic corticosteroids in 60% and 17% of patients, respectively. Secondary immunosuppression with infliximab (2%) and mycophenolic acid (1%) was also required in patients treated with nivolumab plus ipilimumab.[5]

[Table 1]: Highlights of Key Outcomes among Intermediate or Poor Risk Patients[2]

A: Progressions free survival and overall survival in the intermediate and poor risk population

| | **Nivolumab plus Ipilimumab N=425** | **Sunitinib N=422** |
|---|---|---|
| **Overall Survival** | | |
| Number of events, n (%) | 140 (32.9) | 188 (44.5) |
| Median OS (months), (95% CI) | NR (28.2-NE) | 26 (22.1-NE) |
| HR (98% CI) | 0.63 (0.44-0.89) | |
| p-value | 0.001 | |
| **Progression Free Survival** | | |
| Number of events, n (%) | Not available | Not available |
| Median PFS (months), (95% CI) | 11.6 | 8.4 |
| HR (99.1% CI) | 0.82 (0.64-1.05) | |
| p-value | P=0.03 | |

B: Response rate in the intermediate and poor risk population

| **Variable** | **Nivolumab plus Ipilimumab (N=425)** | **Sunitinib (N=422)** |
|---|---|---|
| Confirmed objective response rate — % (95% CI)† | 42 (37–47)‡ | 27 (22–31)‡ |
| Confirmed best overall response — no. (%)† | | |
| Complete response | 40 (9)‡§ | 5 (1)‡§ |
| Partial response | 137 (32) | 107 (25) |
| Stable disease | 133 (31) | 188 (45) |
| Progressive disease | 83 (20) | 72 (17) |
| Unable to determine or not reported | 32 (8) | 50 (12) |
| Median time to response (range) — mo | 2.8 (0.9–11.3) | 3.0 (0.6–15.0) |
| Median duration of response (95% CI) — mo | NR (21.8–NE) | 18.2 (14.8–NE) |
| Patients with ongoing response — no./total no. (%) | 128/177 (72) | 71/112 (63) |

* NE denotes not estimable, and NR not reached.
† Response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent radiology review committee.
‡ P<0.001 for the difference between groups.
§ The analysis of the between-group difference in complete response was exploratory.

CI: confidence interval, HR: hazard ratio, OS: overall survival, PFS: progression free survival

From The New England Journal of Medicine, Motzer RJ, Tannir NM, McDermott DR, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, Volume 378, Page 1283. Copyright © 2018. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

### 1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

***Patient Advocacy Group Input***

One patient advocacy group, Kidney Cancer Canada (KCC), provided input on nivolumab-ipilimumab for the treatment of patients with renal cell carcinoma review. To capture the patient and caregiver experience, KCC conducted an online survey and collected information from 196 respondents (160 patients and 36 caregivers). Based on KCC, mRCC is highly burdensome to patients due to its poor prognosis, particularly to patients with intermediate- and poor-risk status as their overall survival is much lower than patients with favourable-risk. mRCC significantly impacts quality of life, and patients often face eventual resistance to first-line therapies; overall, KCC highlights an unmet need for effective first-line therapies that result in meaningful benefit in overall survival.

Respondents indicated that treatments they had undergone were relatively tolerable. However, nearly one quarter of individuals indicated that current treatment options were not at all tolerable, indicating a need for alternative therapies. KCC highlighted the need for choice in treatment options, which would benefit both clinicians and patients. When considering new therapies, respondents indicated a need for new drugs, or new drug combinations that result in fewer side effects as being of great priority. Based on the patient advocacy input, respondents would like to have drug treatments that combat the negative impact RCC has on quality of life.

Among three patients who reported having experience with nivolumab plus ipilimumab, patients indicated nivolumab plus ipilimumab as being more tolerable than drug treatments they had previously been prescribed; while the assessment of tolerability was inferred from only three patients, KCC mentioned that this was in line with results from the Checkmate 214 trial. The patients reported that nivolumab plus ipilimumab was extremely effective as a therapy, one patient even indicating having no evidence of disease. Two of the three patients provided input regarding side effects; among the two, both indicated that the benefits of nivolumab plus ipilimumab outweighed the experienced side effects. Two of three patients provided input regarding the impact of nivolumab plus ipilimumab on their quality of life; patients mentioned positive impacts on their quality of life, with statements that reflected hopeful outlooks.

Please see Section 3 for more details.

***Provincial Advisory Group (PAG) Input***

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with oral targeted therapies
- Retreatment with nivolumab + ipilimumab after progression
- Clarity on criteria for determining risk

Economic factors:

- Drug wastage

- Resources required to administer intravenous infusion, monitor and treat infusion related reactions and monitor and treat adverse events

Please see Section 4 for more details.

### *Registered Clinician Input*

The clinicians providing input reported that there is an unmet need for treatment for poorer risk patients with metastatic renal cell carcinoma. It was noted that nivolumab-ipilimumab would be used specifically for the intermediate/poor risk population because other treatments are effective in better prognosis patient populations. The clinicians commented on the positive trial results and noted that overall survival was improved with nivolumab-ipilimumab compared to sunitinib, and recognized that nivolumab ipilumumab has manageable toxicity profile. In terms of sequencing, the clinicians providing input indicated that nivolumab-ipilimumab would be given as first line treatment with other therapies given subsequently. There is no companion diagnostic required to receive this therapy.

Please see section 5 for more details.

### *Summary of Supplemental Questions*

There were no supplemental questions identified for this review.

### *Comparison with Other Literature*

Through the systematic review of the literature, a phase I, open-label, parallel-cohort, dose-escalation study, CheckMate 016, was identified. Safety data from this study was included included in this section as supporting evidence for safety outcomes reported in checkmate 214.

See Section 8 for further details on the comparison with other literature section.

### 1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for nivolumab plus ipilimumab for previously untreated advanced or metastatic renal cell carcinoma.[2,8]

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>Histologic type of disease</td><td>The CheckMate 214 trial limited its inclusion criteria to patients with confirmed clear cell RCC.</td><td>Are the trial results generalizable to other types of RCC (i.e., non-clear cell carcinoma)?</td><td>The CGP noted that in general patients with non-clear cell RCC are managed the same way as patients with clear cell RCC. The CGP therefore agree that patients with non-clear cell histology should be eligible for treatment with nivolumab plus ipilimumab in this setting. Furthermore, although trials are forthcoming in this population results will take longer to report as the patient population is smaller.</td></tr>
<tr><td>Karnofsky Performance Status (KPS)</td><td>Inclusion criteria specified patients were required to have a KPS ≥70.</td><td>Do the results apply to patients with KPS <70?</td><td>The CGP agree that it is reasonable to generalize the trial results to patients with KPS<70 at the discretion of the treating oncologist. The CGP note that concerns related to tolerability are not relevant with immunotherapies as they are well tolerated agents. Such considerations have more importance with chemotherapies.</td></tr>
<tr><td>Biomarkers</td><td>Exploratory analyses results of baseline PD-L1 tumour expression showed a hazard ratio for death of 0.73 for PD-L1 expression <1% and 0.45 for expression ≥1%.<br><br><table><tr><th>Baseline PD-L1 expression</th><th>Nivo+ ipi</th><th>Sunitinib</th><th>HR for Death (95% CI)</th></tr><tr><td>PD-L1-<1%</td><td>93/284</td><td>114/278</td><td>0.73 (0.56-0.96)</td></tr><tr><td>PD-L1 ≥ 1%</td><td>28/100</td><td>57/114</td><td>0.45 (0.29-0.71)</td></tr><tr><td>Not reported</td><td>19/41</td><td>17/30</td><td>0.75 (0.39-1.45)</td></tr></table></td><td>Are there expected differences in effect based on biomarker status? Are the results applicable to all subgroups equally?</td><td>There is insufficient evidence to conclude that PD-L1 expression level predicts for improved OS. The CGP agree that the use of nivolumab plus ipilimumab should not be based on PD-L1 expression levels.</td></tr>
<tr><td>Autoimmune disorders and/or</td><td>Patients with autoimmune disease or those with any condition requiring systemic treatment with</td><td>Do the results apply to patients with</td><td>The CGP note that an emerging body of evidence supports the safe use of immunotherapies in this</td></tr>
</table>

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | treatment with systemic cortico-steroids | corticosteroids (>10 mg daily Prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug were excluded | existing active autoimmune diseases or those with a condition for which they're treated with systemic cortico-steroids? | population and agree that the use of nivolumab plus ipilimumab in patients with autoimmune disease or any condition requiring systemic corticosteroids be left to the discretion of the treating oncologist. |
| | Metastatic Sites | Patients with CNS metastases were excluded from the trial, but an ongoing trial (CheckMate 920) is currently investigating nivolumab plus ipilimumab in patients with non-active brain metastases. | Are the CheckMate 214 trial results generalizable to patients with non-active brain metastases? | The CGP noted that patients with RCC and who have brain metastases are different from patients on the CheckMate 214 trial. The CGP further noted a desire to be able to use nivolumab plus ipilimumab in patients with CNS metastases given evidence in other indications (i.e., melanoma) which supports the activity of this combination agent in the brain. The CGP acknowledge that the results of the CheckMate 920 trial will verify the efficacy of the combination therapy in this population. |
| **Intervention** | Pazopanib | The CheckMate 214 trial compared nivolumab plus ipilimumab to sunitinib. There was no direct or indirect evidence comparing to pazopanib, a relevant comparator. | Are the results of the CheckMate 214 trial generalizable to patients who may receive pazopanib? | Although the CheckMate214 trial only compared to sunitinib and there were no direct or indirect comparison made to pazopanib, the CGP agree that the results observed with sunitinib are generalizable to treatment with pazopanib. |

### 1.2.4 Interpretation

#### *Burden of Illness and Need*

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6600 new cases and 1,900 deaths due to the disease.[9] About 85% of kidney cancers are renal cell cancers (RCC), which are genetically and histologically distinctly different from carcinomas arising from the renal pelvis, which are known as urothelial carcinomas (UC). At presentation, 75% of patients with RCC will have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases), while about 25% are already metastatic. Among patients with metastatic disease, 75% will have intermediate or poor prognosis. Of the patients diagnosed with localized disease, 50% of patients will eventually relapse and metastasize. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly to 50-60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured.[10]

The most commonly used classification for mRCC in the era of immunotherapy was the MSKCC criteria which include the presence or absence of five distinct risk factors (performance status, lactate dehydrogenase, corrected calcium, hemoglobin, and time from diagnosis to treatment). This classification has been used both in routine practice to determine prognosis and as part of the eligibility criteria for clinical studies. The IMDC criteria describes a more extensive prognostic risk model and has been shown to improve in predicting prognosis as compared to the MSKCC, CCF(Cleveland Clinic Foundation) model and the IKCWG(international Kidney Cancer Working Group) model. Both, the MSKCC and IMDC models are used in Canada

Targeted therapies have largely replaced older immunotherapies as standard treatment for patients with metastatic disease and today, high-dose interleukin-2 is only considered for a highly selected, very small subgroup of patients, while low-dose interferon and interleukin-2 as single agents are not recommended at all.[11] Sunitinib and pazopanib, both small molecule tyrosine kinase inhibitors of the vascular-endothelial-growth-factor (VEGF) receptor are considered the standard treatment options in the first-line setting.[12,13] Although temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria,[14] this agent is rarely used in the Canadian setting. Although there are standard treatment options in this setting, there is a need for more effective options that prolong survival and have better toxicity profile

#### *Effectiveness*

Based on the primary analysis of the CheckMate 214 trial, in patients with intermediate- and poor-risk RCC, the median OS was not reached in the nivolumab and ipilimumab arm and was 26.0 months in the sunitinib arm (HR, 0.63; 99.8% CI, 0.44-0.89; *P* <.0001). After the first interim analysis, the trial was stopped by the data monitoring committee for superiority. PFS in the intermediate and poor risk group was 11.6 months vs 8.4 months (HR, 0.82; 99.1% CI, 0.64-1.05; *P* = 0.0331) with a P value of 0.009 required for significance. The ORR (overall response rate) was 42% vs 27% (*P*< 0.001) in the intermediate and poor risk patients. Median duration of response has still not been reached with combination immunotherapy versus 18.2 months for sunitinib.

In the overall population, the median overall survival (OS) was not reached with the combination versus 32.9 months with sunitinib (HR, 0.68; 99.8% CI, 0.49-0.95; *P* = .0003). The median PFS was not improved – 12.4 vs 12.3 months (HR 0.98; 99.1% CI, 0.79-1.23; *P* =0.8498). The ORR (overall response rate) was 39 versus 32% (p=.0191) in the overall ITT population. The median duration of response was significantly superior with nivolumab/ipilimumab compared with sunitinib (not reached vs 18.2 months**).** There was no benefit for the combination versus sunitinib in those with a favorable risk. The registered clinician input noted that there were data suggesting that sunitinib has better efficacy in patients with favourable risk. The CGP note that this was an underpowered exploratory analysis. Therefore, a conclusive statement cannot be made on the superior efficacy of sunitinib in this population. An exploratory analysis of outcomes by PD-L1 expression status suggests that PD-L1 expression may be prognostic of worse outcomes; however, the ability of PD-L1 expression status to predict improved surivial or response to nivolumab plus ipilimumab is unclear. Hence the role of PD-L1 expression as a predictive biomarker for response remains unclear.

Health related quality of life was an exploratory outcome in the trial and descriptive analysis were presented. Improvements were reported at most measurement time points for both questionnaires used. It is unclear if minimally important differences were met.

### *Safety*

Safety outcomes were consistent in between the intermediate/poor risk patients and all treated patients. The proportion of grade ≥3 was lower in the nivolumab + ipilimumab group (46%) compared to the sunitinib group (63%). The most common grade 3 or 4 adverse effects for the combination were lipase increase (10.2%), fatigue (4%) and diarrhea (4%) while for sunitinib, they included fatigue (9%), diarrhoea (5%), lipase increase (7%), anemia (5%), hypertension (16%), palmar plantar (9%) and thrombocytopenia (5%). Drug related adverse events lead to discontinuation in 22% of patients in the combination group and 12% in the sunitinib group. Drug related serious AE's of all grades (30% versus 15%) or of grades 3 or 4 (22% versus 12%) were greater in the combination group compared to sunitinib, respectively. Immune-mediated adverse events occurred in 436 patients treated with nivolumab plus ipilimumab and included skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories. Of these, 152 (35%) received high-dose glucocorticoids. Concomitant immune-modulating medications (IMMs) were administered for management of AEs in 72% of patients in the nivolumab plus ipilimumab arm and 33% of patients in the sunitinib arm. (Tannir poster) IMM included systemic corticosteroids in 60% and 17% of patients, respectively.

### *Other considerations*

The availability of nivolumab plus ipilimumab in the first line setting raises questions on the appropriate sequencing of subsequent agents. Some evidence was made available through the CheckMate214 trial through follow up of patients on subsequent agents patients received. Although this evidence is of some interest, the CGP agreed that it is not sufficient to make a conclusive statement on sequencing of agents following progression on nivolumab plus ipilimumab. The CGP agree that it is reasonable to treat patients with TKI's subsequent to progression on nivolumab plus ipilimumab however the choice of agent to be

used should be left to the discretion of the treating clinician. This is in alignment with input from registered clinicians.

## 1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to the combination of nivolumab plus ipilimumab for intermediate and poor risk metastatic and advanced renal cell carcinoma of clear cell histology. This conclusion is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival for nivolumab plus ipilimumab compared to sunitinib. In the trial, frontline treatment with the combination of nivolumab and ipilimumab reduced the risk of death by 37% compared with sunitinib for patients with mRCC.

In making this conclusion the Clinical Guidance Panel also considered that:

- Nivolumab plus ipilimumab combination treatment is likely to be the standard first line treatment in this patient population. This is supported by input from registered clinicians.
- Although the CheckMate214 trial only compared to sunitinib and there were no direct or indirect comparison made to pazopanib, the CGP agree that the results observed with sunitinib are generalizable to treatment with pazopanib.
- Patients should be eligible for treatment with nivolumab plus ipilimumab if they have RCC with clear cell component, have not been previously treated with an immunotherapy in the metastatic setting (including adjuvant and neoadjuvant). Following the posting of the pERC Initial Recommendation, the CGP further noted that in general patients with non-clear cell RCC are managed the same way as patients with clear cell RCC. The CGP therefore agree that patients with non-clear cell histology should be eligible for treatment with nivolumab plus ipilimumab in this setting. Furthermore, although trials are forthcoming in this population results will take longer to report as the patient population is smaller.
- There is uncertainty on the optimal sequencing of available agents following first line treatment with the combination agent.
- As done in the CheckMate 214 trial, the IMDC risk score may be used to determine patients risk status. The CGP agree this is now the standard practice in Canadian settings.
- Based on the regulatory approval granted by Health Canada, the CGP agreed that it is reasonable to administer nivolumab as a weight based dose of 3mg/kg up to 240mg every 2 weeks or 6mg/kg up to 480mg every 4 weeks.
- The CGP noted that patients who are currently on a TKI and tolerating the treatment well will likely be kept on treatment until disease progression after which nivolumab single agent would be used as second line treatment. Unless patients are not tolerating treatment well, treating clinicians are more likely to opt for optimizing the available treatment options and keep patients on a TKI instead of switching patients to nivolumab plus ipilimumab.
- Nivolumab plus ipilimumab is a well-tolerated agent compared to TKI's which have greater toxicity with long term use. Discontinuation due to adverse events and immune related adverse events were however greater in the combination group.

- For patients who take a treatment break and have disease progression, there is no evidence for or against the efficacy of re-starting nivolumab monotherapy. The opinion of the CGP is that a re-challenge would be appropriate with close follow-up to ensure that the treatment is still working. Following the posting of the pERC Initial Recommendation, the CGP further noted that treatment starting and stopping did not occur frequently in the trial although it is expected to occur more frequently in clinical practice. It is however more likely that only the maintenance monotherapy with nivolumab would be re-started as there is very little data to guide management of treatments once patients progress during a treatment break. The CGP do acknowledge that if the treatment break was sufficiently long, there may be rationale to restarting both drugs.

# 2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

## 2.1 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6600 new cases and 1,900 deaths due to the disease.[9] About 85% of kidney cancers are renal cell cancers (RCC), which are genetically and histologically distinctly different from carcinomas arising from the renal pelvis, which are known as urothelial carcinomas (UC). About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers and include papillary and chromophobe subtypes amongst others. At presentation 75% of patients with RCC will have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases), while about 25% are already metastatic. Among patients with metastatic disease, 75% will have intermediate or good prognosis. Of the patients diagnosed with localized disease, 50% of patients will eventually relapse and metastasize. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly to 50-60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured.[10]

Metastatic RCC is considered refractory to both conventional cytotoxic chemotherapy and conventional radiation therapy. Historically, older immunotherapy approaches like cytokines such as interferon or interleukin were the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit and toxicity was an issue. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[15-17] several key prognostic factors have been identified in patients with metastatic disease that can divide metastatic patients into favourable, intermediate or poor risk groups. The most commonly used classification for mRCC in the era of immunotherapy was the MSKCC criteria which include the presence or absence of five distinct risk factors (performance status, lactate dehydrogenase, corrected calcium, hemoglobin, and time from diagnosis to treatment). This classification has been used both in routine practice to determine prognosis and as part of the eligibility criteria for clinical studies. More recently, the IMDC (The International Metastatic Renal Cell Carcinoma Database Consortium) criteria which better reflects treatment with targeted agents has come into regular use and for the purposes of clinical trials.[18-20]

Advances in our understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents), in particular for the clear-cell subtype of RCC, have resulted in the availability of a number of new treatment options for patients with metastatic RCC. Clear-cell carcinomas are characterized by the presence of inactivating mutations in the von-Hippel-Lindau gene. Loss of functional VHL protein results in the activation of pro-angiogenic and growth factor pathways via constitutive stabilization of the alpha subunits of a group of transcriptionally active proteins called the hypoxia-inducible factors (HIF).[21] HIF plays a central role in renal tumorigenesis by acting as a transcription factor for genes that are involved in angiogenesis, tumor cell proliferation, cell survival and progression, metastatic spread, apoptosis and glucose metabolism. The phosphatidylinositol-3 kinase (PI3K)-AKT-mTOR signal transduction

pathway is also involved in controlling HIF. Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR pathways. Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and also have a different toxicity profile.

Over the past few years, the RCC treatment landscape has changed significantly and continues to evolve rapidly. While these therapies are active in clear cell RCC, the vast majority of tumours eventually become treatment refractory through different, as yet poorly understood, mechanisms. To date, there are no curative treatment options for metastatic RCC.

## 2.2 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced disease. There is currently no role for neoadjuvant therapy. Studies evaluating the use of adjuvant therapy have shown mixed results. But, on the basis of the recent S-TRAC study evaluating adjuvant sunitinib in high risk RCC patients, which showed a disease-free survival benefit, despite excess toxicity, the FDA has approved adjuvant sunitinib in high risk patients.[22]

In the setting of metastatic disease, until the introduction of targeted therapies, immunotherapy (cytokines) with low dose interferon-α, low dose interleukin-2 or high dose interleukin-2 represented the standard of care. Although these agents were helpful for a small subset of patients, the majority of patients derived no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity. Targeted therapies have largely replaced older immunotherapy as standard treatment for patients with metastatic disease and today, high-dose interleukin-2 is only considered for a highly selected, very small subgroup of patients, while low-dose interferon and interleukin-2 as single agents are not recommended at all.[11]

There are currently three different classes of agents in routine clinical use in Canada for the treatment of metastatic clear-cell RCC: small molecule tyrosine kinase inhibitors (TKIs) such as sunitinib, pazopanib; inhibitors of mTOR (mammalian target of rapamycin) such as temsirolimus or everolimus; and the monoclonal antibody bevacizumab in combination with interferon. All of these agents interfere with the VEGF pathway and cell signalling, which plays a crucial role in tumour angiogenesis. Tyrosine kinase inhibitors block the intracellular domain of the VEGF receptor, while bevacizumab binds VEGF and mTOR inhibitors interfere with mTOR, which is key regulator within cells including the VEGF pathway. Bevacizumab/interferon has never been filed for approval in Canada and will therefore not be included in the discussion of the current treatment landscape.

Current treatment landscape:

Sunitinib and pazopanib, both small molecule tyrosine kinase inhibitors of the vascular-endothelial-growth-factor receptor are considered the standard treatment options in the first-line setting.[12,13] Sunitinib demonstrated a more than doubling in progression-free survival (PFS) compared to the standard of care at the time, interferon. Sunitinib was also the first drug to lead to a median overall survival of more than 2 years in the metastatic setting. Pazopanib was shown to be non-inferior to sunitinib in a large randomized phase III trial. For poor risk patients (according to the MSKCC criteria) the mTOR inhibitor temsirolimus, given intravenously once a week, was tested in a randomized trial against

interferon and demonstrated superior overall survival outcomes as compared to interferon alone or the combination of both drugs. Although temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria,[14] this agent is rarely used in the Canadian setting.

Second Line

After failure of first-line TKI therapy, everolimus, an oral mTOR inhibitor and axitinib, a VEGFR-TKI have both been evaluated and were approved based on a PFS benefit. [23-26] In the RECORD1 trial in patients failing at least one prior line of TKI therapy Everolimus showed a significant PFS benefit over placebo (4.9 vs.1.9 months; HR 0.32).[24] In the AXIS study, in a similar population, Axitinib showed a PFS benefit over sorafenib with median a PFS of 6.7 vs 4.7 months (HR 0.67) in the overall group and 4.8 vs 3.4 months (HR 0.74) in sunitinib pretreated patients. Neither of these studies demonstrated a clear overall survival benefit.

Nivolumab is a novel fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor, that blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Blocking this interaction leads to antitumor response via activation of an immune response. Nivolumab was tested against Everolimus in a large open-label phase III study (Checkmate 025) of 821 mRCC patients failing at least one line of TKI therapy. The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The confirmed response rates were 21.5% versus 3.9%; median durations of response were 23.0 versus 13.7 months.[27,28]

Although now approved in second line, there is still a majority of patients that will not respond to Nivolumab, or will respond and subsequently progress, for whom there are no curative options, underscoring the need for new treatment strategies.[29] Strategies based on overcoming resistance mechanisms to current agents maybe particularly effective. One of these agents is Cabozantanib. This is an oral small molecule inhibitor of multiple tyrosine kinase receptors with activity toward VEGF receptor 2 (VEGFR-2) and MET (hepatocyte growth factor receptor), but also targets RET (rearranged during transfection), KIT (mast/stem cell growth factor receptor), AXL, TIE2 (angiopoietin receptor) and FLT3 (Fms-like tyrosine kinase), which are important mediators of tumor cell survival, metastasis and tumor angiogenesis

## 2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of nivolumab plus ipilimumab for patients with the following criteria:

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell component
- Previously untreated with systemic therapy for RCC.

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

## 2.4 Other Patient Populations in Whom the Drug May Be Used

Patients with non-clear cell renal cell carcinoma represent a particularly difficult group. Non-clear cell renal cell carcinoma includes papillary, collecting duct, chromophobe and a number of other kidney cancer subtypes. Due to the heterogeneity and small patients numbers larger studies are extremely difficult to complete. Today, most of these patients are treated according to clear cell cancer guidelines despite the lack of large randomized studies.

# 3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Kidney Cancer Canada (KCC), provided input on the use of nivolumab-ipilimumab for the treatment of patients with intermediate or poor risk metastatic renal cell carcinoma (mRCC). To capture the patient and caregiver experience, KCC conducted an online survey in both English and French that was sent to patients and caregivers from April 20, 2018 to May 1, 2018. A total of 196 respondents completed the survey; 172 responded to the English version of the survey and 24 responded to the French version. The surveys contained three types of questions: free-form commentary, scoring options and limited closed questions, and covered content on experience with RCC and expectations for therapies including nivolumab-ipilimumab.

A total of 196 respondents completed surveys. The majority of respondents (98.5%; n=193) were Canadian and represented all ten provinces and one territory; while the remaining respondents were from the US (n=2), France (n=2), Belgium (n=1) and Taiwan (n=1). The majority of respondents were currently living with kidney cancer (37.2%; n=73) or were kidney cancer survivors (44.4%; n=87); and additional respondents (18.4%; n=36) were caregivers. Three respondents indicated having experience with nivolumab-ipilimumab.

Based on the patient input received from KCC, mRCC is highly burdensome to patients due to its poor prognosis, particularly to patients with intermediate- and poor-risk status as their overall survival is much lower than patients with favourable-risk. mRCC significantly impacts quality of life, and patients often face eventual resistance to first-line therapies; overall, KCC highlighted an unmet need for effective first-line therapies that result in meaningful benefit in overall survival.

Respondents in this sample indicated that treatments they had undergone were relatively tolerable. However, nearly one quarter of individuals responded that current treatment options were not at all tolerable, indicating a need for alternative therapies. KCC highlighted the need for choice in treatment options, which would benefit both clinicians and patients. When considering new therapies, respondents indicated a need for new drugs, or new drug combinations that result in fewer side effects as being of great priority. Based on the patient advocacy input, respondents would like to have drug treatments that combat the negative impact RCC has on quality of life.

Among the three respondents who reported having experience with nivolumab-ipilimumab, they indicated nivolumab-ipilimumab as being more tolerable than drug treatments they had previously been prescribed. While the assessment of tolerability was inferred from only three respondents, KCC noted that this was in line with results from the Checkmate 214 trial. The respondents reported that nivolumab-ipilimumab was extremely effective as a therapy, one respondent indicated having no evidence of disease. Two of the three respondents provided input regarding side effects; among the two, both indicated that the benefits of nivolumab-ipilimumab outweighed the experienced side effects. Two of three respondents provided input regarding the impact of nivolumab-ipilimumab on their quality of life; they mentioned positive impacts on their quality of life, with statements that reflected hopeful outlooks.

Please see below for a summary of specific input received from KCC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

## 3.1 Condition and Current Therapy Information

### 3.1.1 Experiences Patients have with RCC

As stated by KCC, mRCC is fatal with no known cure, and is associated with a high burden of illness due to its poor prognosis. KCC emphasized its impact on quality of life; patients withstand great morbidity, and as the disease progresses, patient quality of life deteriorates. Weakness, fatigue and shortness of breath are symptoms reported by KCC to be the main drivers of poor quality of life whether it be due to the disease or the treatments provided to combat mRCC.

KCC focused on the lack of effective treatment options available for patients once they experience resistance to treatment beyond first-line. Second-line therapies that effectively combat some of the drug resistance experienced by patients do exist, however KCC stated that improved treatments with meaningful overall survival benefit were needed in the first-line. KCC posits that there is significant unmet need for patients with mRCC, and that existing treatments are not effective for all patient subgroups. Specifically, patients identified as intermediate- and poor-risk face greater difficulty, as their overall survival is much lower than patients with favourable-risk.

### 3.1.2 Patients' Experiences with Current Therapy for RCC

As reported by KCC, the treatments used to treat kidney cancer among the sample included sunitinib (n=60), cabozatinib (n=4), temsirolimus (n=1), everolimus (n=6), axitinib (n=16), pazopanib (n=16), sorafenib (n=3), nivolumab (n=26), high dose interleukin-2 (Il-2) (n=4), and other (n=22). Respondents were asked to rate the side effects of their treatments on a scale from 1 to 5 (1 being "completely intolerable" and 5 being "very tolerable") (Table 2). KCC reported a weighted average of 3.29 among 74 respondents; which suggests most respondents thought current systemic treatments were generally tolerable. However, almost one quarter of respondents recorded responses of either "1" or "2", which suggests that a relatively significant proportion of respondents consider current therapies to be intolerable.

Table 2: Survey respondents' (n=74) self-reported ratings regarding treatment side effects.

| 1 – Completely Intolerable | 2 | 3 | 4 | 5 – "Very Tolerable" | Total | Weighted Average |
|---|---|---|---|---|---|---|
| n=3 (4.05%) | n=15 (20.27%) | n=29 (39.19%) | n=18 (24.32%) | n=9 (12.16%) | n=74 | 3.29 |

KCC highlighted recurring themes between this submission for nivolumab-ipilimumab for RCC, and previous submissions for kidney cancer in 2011, 2012, and 2016 for pazopanib, axitinib and nivolumab, respectively. The recurring themes included a requirement for better treatment options, since current treatment options are not effective for everyone; and secondly, when considering new therapy, having a choice in treatment options was deemed very important, including the opportunity to make an informed decision based on known side effects.

Finally, KCC posits that treatment choice and patient preference must be considered when assessing the value of a new drug. Further, for patients who experience drug intolerance, providing treatment alternatives within lines of therapy are extremely important.

## Improved Outcomes

Using close-ended questions, KCC asked respondents to rank five treatment priorities, such as screening or delaying progression for example, for RCC on a scale from 1 to5, with 5 being the highest priority. Table 3 displays the results of the respondents' priority rankings.

Table 3: Survey respondents' self-reported priority rankings for treatment for RCC

| Treatment Priorities | Priority Ranking n (%) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | Score |
| We need drugs or drug combinations with fewer side effects than currently available drugs | 15<br>9.74% | 13<br>8.44% | 24<br>15.58% | 38<br>24.66% | 64<br>41.56% | 3.8 |
| We need drugs that do better at delaying disease progression | 9<br>5.84% | 38<br>24.68% | 49<br>31.82% | 41<br>26.62% | 17<br>11.04% | 3.12 |
| We need better ways to identify the best drug treatment for each individual patient/disease situation (biomarkers) | 10<br>6.54% | 47<br>30.71% | 37<br>24.18% | 35<br>22.88% | 24<br>15.69% | 3.11 |
| We need ways of detecting kidney cancer earlier (screening) | 76<br>46.91% | 14<br>8.64% | 11<br>6.79% | 17<br>10.49% | 44<br>27.16% | 2.62 |
| We need drugs or drug combinations that have greater effect on slowing or stopping the spread of kidney cancer in the body (metastasis) | 47<br>30.13% | 40<br>25.64% | 29<br>18.59% | 22<br>14.10% | 18<br>11.54% | 2.51 |

Based on respondents' ratings in Table 3, respondents rated a need for drugs or drug combinations with fewer side effects (compared to currently available treatments) as being the highest priority. This treatment priority had the greatest proportion of individuals choosing a score of 5 compared to the other listed priorities. The lowest priority identified, relative to the other options provided, was screening and delayed metastasis. . By prioritizing treatments resulting in the reduction of side effects, it appears that, respondents place greater priority on improved quality of life than delaying of disease progression.

KCC indicated there remains many gaps in the management of RCC, along with a significant unmet need for treatment options that offer ongoing/durable response and

increase survival for patients with RCC, the most common type of kidney cancer. Consequently, existing treatments still fail many patients with advanced disease. That being said, KCC did note that new treatments and improved sequencing are starting to offer more durable responses and increased survival for some patients with the treatment paradigm for mRCC undergoing rapid change, KCC indicated there is great promise for significant improvements in the treatment for mRCC.

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for and Experiences To Date with nivolumab plus ipilimumab

As mentioned previously, three respondents reported having experience with the combination of nivolumab-ipilimumab. Using a Likert scale from 1 to 5, with 1 indicating "completely intolerable" and 5 indicating "very tolerable", respondents were asked to rate the side effects of nivolumab-ipilimumab. Previously it was mentioned in that the weighted average for tolerability of drugs used by respondents was 3.29 (Table 2). The weighted average for tolerability using nivolumab-ipilimumab among the three patients with experience was reported to be 3.67. The weighted average for tolerability of nivolumab-ipilimumab is greater than the weighted average of tolerability for other drugs used by respondents, suggesting a greater tolerability for nivolumab-ipilimumab compared to drugs previously used by patients. KCC cautioned this small sample may not in itself provide compelling evidence of nivolumab-ipilimumab combination therapy being more tolerable than, for instance, targeted anti-angiogenesis agents. However, it also aligns with the evidence from the Checkmate 214 trial where patient reported outcomes were used to measure health-related quality of life using the EQ-5D. In the Checkmate trial, patients in the nivolumab-ipilimumab group reported numerically greater scores (compared to baseline) in mobility, self-care, activity, pain, and anxiety (all five domains in the EQ-5D) than the sunitinib group.

KCC also asked the three respondents whether side effects experienced as a result of nivolumab-ipilimumab were outweighed by the benefits of the treatment. Two out of three respondents provided answers to this question, and both indicated that the benefits outweighed the experience of side effects due to nivolumab-ipilimumab. Respondents were also asked to rate how effective they thought nivolumab-ipilimumab was at controlling their kidney cancer using a scale from 1 to 5, with 1 indicating "not effective" and 5 indicating "extremely effective". All three respondents rated the effectiveness of nivolumab-ipilimumab as extremely effective with a rating of 5; one patient further explained that they were currently showing no signs of disease, and another patient reported that their progression had slowed. The respondent who reported no signs of disease provided some additional information, stating "Diagnosed as stage 4 with Mets to lungs. Lucky to be involved in clinical trial and have a positive response. Currently NED and hope for more treatment options in future."

When asked to rate quality of life while taking nivolumab-ipilimumab on a scale from 1 to 5, with 1 indicating "low quality of life" and 5 indicating "high quality of life", two respondents gave a rating of 4 out of 5. These respondents were then asked to provide

comments about how patients thought nivolumab-ipilimumab changed, or was expected to change, their long-term health and well-being. The following are comments from the patient respondents:

*"With the exception of extreme side effect at approximately six months, it has enabled me to carry on a fairly normal lifestyle"*

*"More energy, maintain active lifestyle. Positive outlook, hope."*

## 3.3 Additional Information

KCC provided a statement that the current realm of kidney cancer treatments is rapidly changing, with the potential of additional treatments and clinical trials emerging. KCC reminded that nivolumab was approved as a second-line option for kidney cancer, and the pCODR would soon be reviewing cabozantinib in second-line, lenvatinib in combination with everolimus in the second-line, in addition to the current review of nivolumab in combination with ipilimumab for first-line treatment of intermediate and poor risk patients.

KCC acknowledged that with the rapid onboarding of new treatments, there may be lack of clarity in regards to optimal sequencing and that this may prove challenging for health technology assessment (HTA) bodies. However, KCC emphasized that new treatments provide the opportunity for physicians to provide better treatments to patients, and for patients to experience improved outcomes.

KCC urged the pCODR expert review committee to allow the collection of prospective real world data to consider as part of their review, specifically, real world survival data, data regarding side effects and toxicities, cost-effectiveness, and utilization (based on patterns of care and toxicities). By incorporating such data, KCC hopes that the pCODR expert review committee will be able to resolve issues of uncertainty it may encounter during their review of the clinical data for any current and forthcoming treatments for RCC.

KCC then provided a list of organizations that could aid in providing both prospective and retrospective data pCODR may find pertinent to reviews, such as Kidney Cancer Research Network of Canada (KCRNC), which can provide real world evidence that may resolve issues HTA committees may face during a review, and Canadian Kidney Cancer information system (CKCis), a national web-based registry containing retrospective and prospective data from consenting patients with RCC. CKCis, which has been in operation for over six years, contains mature enough data to result in several key publications of manuscripts, with more expected in the future. CKCis and KCRNC are in collaboration, as CKCis is now central to the activities of KCRNC.

KCC highlighted that CKCis was previously used by pCODR to inform the very first Request for Advice (RFA) for the final recommendation of axitinib to answer the following question raised by the Provincial Advisory Group (PAG): "Is there evidence to fund axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma?" For this question, CKCis analysed Time to Treatment Failure (TTF) among

patients pretreated with either sunitinib or pazopanib, where axitinib was provided second-line; it was determined that “axitinib should be considered an option for all patients in Canada post 1stL VEGF-Targeted Therapy without the limitations of the existing pCODR recommendation”. Following this conclusion, the pCODR Clinical Guidance Panel concluded that there was “appropriate real world evidence and expert judgement to justify axitinib as an equal alternative to everolimus in the second line setting.” Through this example KCC wanted to highlight the benefit of using real world data to analyze the effectiveness and value of a drug, and how it can provide added benefit to the HTA process. KCC further stated that they, along with KCRNC, are prepared to collaborate with pCODR to support evidence-building on an ongoing basis for new and existing drugs approved for mRCC.

# 4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with oral targeted therapies
- Retreatment with nivolumab + ipilimumab after progression
- Clarity on criteria for determining risk

Economic factors:

- Drug wastage
- Resources required to administer intravenous infusion, monitor and treat infusion related reactions and monitor and treat adverse events

Please see below for more details.

## 4.1 Currently Funded Treatments

For intermediate risk advanced or metastatic renal cell carcinoma, the current treatments are oral targeted therapies. Pazopanib and sunitinib are funded in all provinces for first-line treatment.

For poor risk advanced or metastatic renal cell carcinoma, temsirolimus is also available in addition to pazopanib and sunitinib.

PAG noted that the Checkmate-214 trial compares nivolumab/ipilimumab combination to sunitinib. PAG is seeking information on comparison to pazopanib and temsirolimus or whether the trial results can be generalized to patients receiving other first line therapies

## 4.2 Eligible Patient Population

PAG is seeking clarity on the eligible patient populations. The reimbursement request is for poor/intermediate risk patients with previously untreated advanced or metastatic RCC with a clear-cell component. Checkmate-214 trial excluded patients previously treated with VEGF inhibitors, VEGF receptor inhibitors and immunotherapies, and enrolled patients with clear cell histology. However, according to the Health Canada approved product monograph, PAG noted that the indication is broader as it does not specify clear cell histology or limit to previously untreated patients. If nivolumab plus ipilimumab is recommended for reimbursement, PAG noted that the trial criteria would be applied to funding criteria. PAG is seeking information on the use of nivolumab plus ipilumumab in previously treated patients and in patients with non-clear cell histology, recognizing these may be out of scope of the current review. PAG is seeking clarity on the scoring (e.g. MSKCC/Motzer, Heng) for determining poor/intermediate risk patients.

PAG noted that the trial allowed patients who had one prior adjuvant or neoadjuvant therapy for completely resectable RCC, if the adjuvant or neoadjuvant therapy did not include VEGF inhibitors or VEGF receptor inhibitors and if the recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. However, it is unclear whether patients who have been treated with immunotherapy in the adjuvant or neo-adjuvant would be included or excluded.

PAG is seeking guidance on whether patients with poor/intermediate risk disease who have started oral targeted therapy and have not yet progressed could be switched to nivolumab/ipilimumab combination as their first-line treatment.

## 4.3 Implementation Factors

PAG has concerns with drug wastage, particularly with ipilumumab which is available in only one vial size. As ipilimumab is available in only one vial strength of 50mg, two vials would be required to prepare a 70mg dose for a 70kg patient and the part vial would be wasted. Drug wastage for nivolumab is minimized with vial sharing as nivolumab is indicated in many other cancers.

PAG is seeking information on alternate dosing schedules for nivolumab in the nivolumab monotherapy phase. PAG is seeking guidance on the use of nivolumab 3mg/kg up to maximum of 240mg every two weeks in the monotherapy maintenance phase, given that this dosing schedule has been adopted in other indications. In addition, PAG is seeking information on the use of nivolumab 6mg/kg up to 480mg every four weeks as the monthly administration schedule would reduce frequency of clinic visits for the patients.

PAG noted that the dose of nivolumab plus ipilimumab combination therapy for renal cancer is different than the dose of the combination for melanoma.

As nivolumab and ipilimumab are intravenous therapies, where as pazopanib and sunitinib are oral therapies, PAG noted that additional resources are required to prepare and administer the two infusions, in addition to chemotherapy chair time and additional clinic visits. Incremental resources are required to monitor and treat infusion reactions, immune related adverse effects and other toxicities associated with immunotherapies.

In the trial, patients continued nivolumab until progression. PAG identified that in clinical practice there are patients who would have treatment breaks and have disease progression during the treatment break. PAG is seeking guidance on restarting nivolumab monotherapy in these patients.

## 4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of oral targeted therapies and immunotherapies. PAG is seeking information on the use of oral targeted therapies after progression on nivolumab/ipilimumab combination therapy.

## 4.5 Companion Diagnostic Testing

PAG noted that the subgroup of patients with PD-L1 expression greater than 1% had better outcomes and is seeking clarity on whether PD-L1 testing is required. PD-L1 status is not

currently being tested in renal cancer patients and is not required for use of nivolumab monotherapy in second line setting.

## 4.6 Additional Information

None.

# 5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided: one from an individual oncologist and one joint submission on behalf of Cancer Care Ontario.

The clinicians providing input reported that there is an unmet need for treatment for poorer risk patients with metastatic renal cell carcinoma. It was noted that nivolumab-ipilimumab would be used specifically for the intermediate/poor risk population because other treatments are effective in better prognosis patient populations. The clinicians commented on the positive trial results and noted that overall survival was improved with nivolumab-ipilimumab compared to sunitinib, and recognized that nivolumab plus ipilumumab has manageable toxicity profile. In terms of sequencing, the clinicians providing input indicated that nivolumab-ipilimumab would be given as first line treatment with other therapies given subsequently. There is no companion diagnostic required to receive this therapy.

Please see below for a summary of specific input received from the registered clinician(s).

## 5.1 Current Treatment(s) for Renal Cell Carcinoma

The clinicians providing input reported that current standard treatments include sunitinib or pazopanib for patients with good to intermediate prognosis, and that treatments for patients with a poor prognosis include temsirolimus, sunitinib or pazopanib.

## 5.2 Eligible Patient Population

The clinicians providing input noted that this funding request is for intermediate to poor risk patients. Currently there are other funded treatments in this disease space. The only approved treatment for poor risk disease is temsirolimus. They noted that in the CheckMate 214 trial, nivolumab-ipilimumab demonstrated superior overall survival and objective response rates compared to sunitinib in intermediate to poor risk patients.

One of the clinician inputs noted that there are patient data not shown in the publication that strongly favours sunitinib as more effective in the “better prognosis” patient population, and this result is not explained. It was noted that the risk category for the current standard of care is MSKCC or its variant and not the mentioned IMDC criteria.

## 5.3 Relevance to Clinical practice

The clinicians providing input felt that this treatment is a “must have” because it is superior to other therapies and has a proven benefit in poor risk patients. They identified that there is an unmet need and in studies in this particular patient population, nivolumab-ipilimumab demonstrated a clear survival advantage over the current standards of care. The clinicians providing input noted that 9% of patients treated with nivolumab-ipilimumab achieved a complete response and there is a clear survival advantage that appears to increase with longer follow-up.

The clinicians providing input reported a manageable toxicity profile of nivolumab-ipilimumab and that the safety profile is consistent with previous studies in multiple tumour types, including advanced RCC. There was a lower incidence of grade 3 and 4 treatment-related

adverse events than observed with sunitinib. They noted that toxicity profile of nivolumab-ipilimumab is different than the current standards of care (e.g. 60% of patients require corticosteroids) but overall quality of life is better with nivolumab-ipilimumab. However, a qualification of the quality of life data is that toxicities from the immune treatment may be more irreversible than toxicities of sunitinib. It should also be noted that the dosing of ipilimumab in RCC is 1mg/kg which is much better tolerated than other studies in other disease sites (e.g. melanoma 3mg/kg.

## 5.4 Sequencing and Priority of Treatments with Nivolumab plus Ipilimumab

The clinicians providing input reported that this immune treatment (nivolumab-ipilimumab) should be given as first line treatment, followed by either targeted therapy or clinical trials. They indicated that better prognosis patients prognosis would not switch from sunitinb to nivolumab-ipilimumab, but patients with poor risk disease would. They identified that if nivolumab-ipilimumab was given first line, then nivolumab monotherapy would not be funded in second/third line, but if sunitinib or pazopanib was given first line, then nivolumab monotherapy could be given for subsequent lines.

## 5.5 Companion Diagnostic Testing

The clinicians providing input noted that the survival benefit was more pronounced in the PD-L1 ≥1% group in the CheckMate 214 trial, but overall, the trial results showed that overall survival was significantly improved with nivolumab-ipilimumab compared to sunitinib across all PD-L1 expression levels. As such, the clinicians providing input indicated that PD-L1 testing is not a requirement for treatment with nivolumab-ipilimumab.

## 5.6 Additional Information

None provided.

# 6 SYSTEMATIC REVIEW

## 6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of nivolumab in combination with ipilimumab in intermediate/poor risk patients with previously untreated advanced or metastatic renal cell carcinoma (RCC).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

## 6.2 Methods

### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

**[Table 3]. Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| Published and unpublished RCTs.<br><br>In the absence of RCTs, fully published non-comparative clinical trials investigating efficacy and safety of nivolumab plus ipilimumab combination therapy should be included. | Previously untreated adult patients with intermediate/poor risk advanced or metastatic RCC. | Nivolumab in combination with ipilimumab | All appropriate treatment regimens including but not limited to:<br>• Sunitinib<br>• Pazopanib<br>• Temsirolimus | <u>Efficacy</u><br>• OS<br>• **PFS**<br>• ORR<br>• DoR<br>• **HRQoL**<br><br><u>Safety</u><br>• **AEs**<br>• SAEs<br>• WDAEs<br>• imAEs<br>Dose adjustment, interruption and/or discontinuation |
| • [Abbreviations] RCT = randomized controlled trial; OS=overall survival; RCC = renal cell carcinoma; PFS = progression-free survival; ORR = objective response rate; DoR = duration of response; HRQoL = health-related | | | | |

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| quality of life; AE = adverse events; SAE = serious adverse events; WDAE = withdrawals due to adverse events; imAEs= immune-mediated adverse events. Bold outcomes were identified as important by patients' input. | | | | |

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

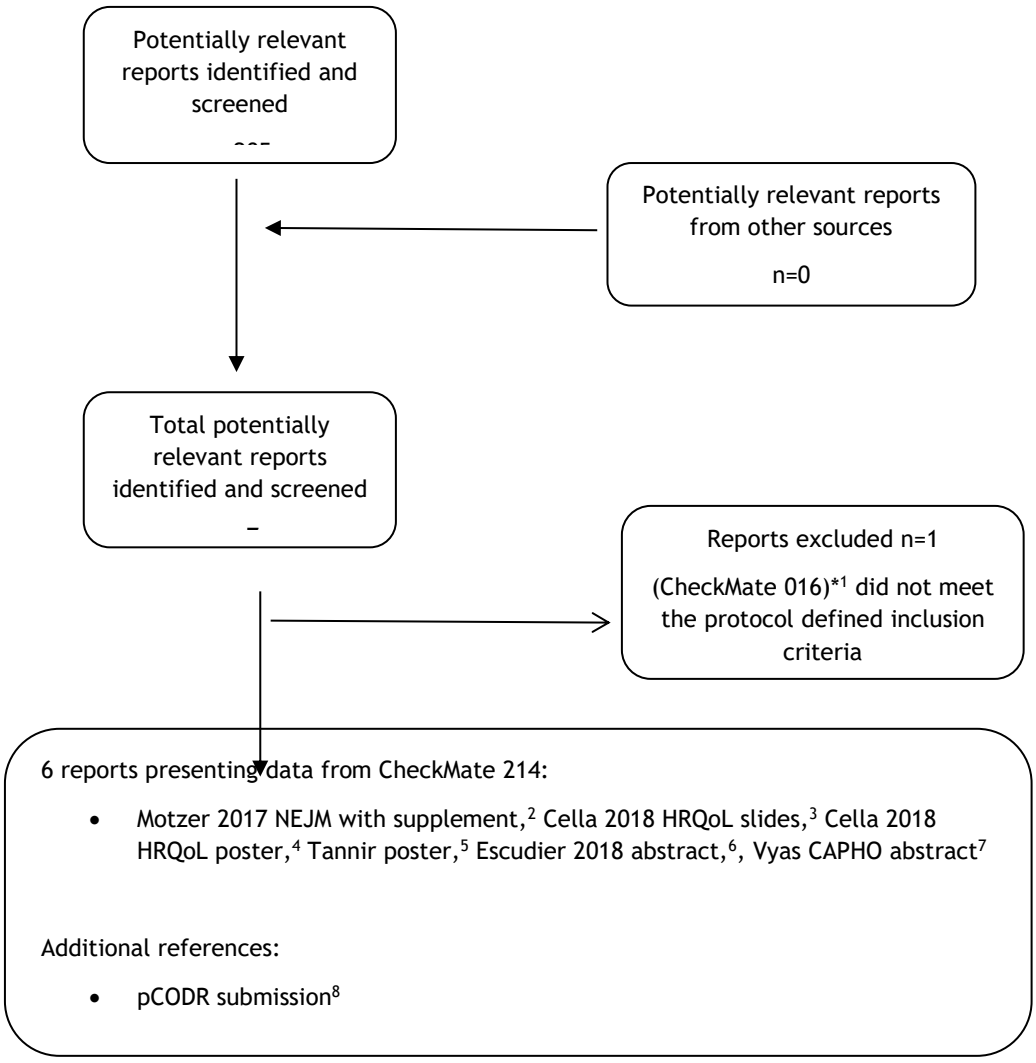
## 6.3 Results

### 6.3.1 Literature Search Results

Of the 285 potentially relevant reports identified, 1 trial with data presented in 6 reports, was included in the pCODR systematic review.[2-5] [6,7]

Through the systematic review of the literature, a phase I, open-label, parallel-cohort, dose-escalation study, CheckMate 016, was identified.[1] It is included in this section as supporting evidence for safety

**Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies**




*Note: Additional data related to study CheckMate 214 were also obtained through requests to the Submitter by pCODR[30]*

** This study was included as supporting evidence for safety and discussed further in Section 8 – Comparison With Other Literature.*

### 6.3.2 Summary of Included Studies

One pivotal clinical trial was identified that met the eligibility criteria and is included in this systematic review (Please see Table 4). CheckMate 214[2] is a phase III, randomized, multicentre open-label study assessing the efficacy and safety of the combination of nivolumab + ipilimumab vs. sunitinib monotherapy in the treatment of adult (≥ 18 years) subjects with previously untreated, advanced or metastatic RCC.

A second, phase I, open-label, parallel-cohort, dose-escalation study, CheckMate 016[1], was identified but did not meet the protocol defined inclusion criteria. This study was however included as supporting evidence for safety and discussed further in Section 8 – Comparison With Other Literature.

#### 6.3.2.1 Detailed Trial Characteristics

**[T able 4]: Summary of Trial Characteristics of the Included Studies**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| CheckMate 214<br>NCT02231749<br>CA209214<br><br>Title: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Sunitinib Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma<br><br>A Randomized Phase III, Open-label Multicentre Study<br><br>Status: Complete<br><br>175 cancer treatment centres in 28 countries from North America, South America, Europe, Australia, and Asia | <u>Key Inclusion Criteria:</u><br>• Age ≥ 18 years<br>• Histological confirmation of RCC with a clear-cell component<br>• Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC<br>• No prior systemic therapy for RCC with the following exception:<br>• One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy<br>• Karnofsky Performance Status (KPS) of at least 70%<br>• Measurable disease as per RECIST1.1<br>• Tumor tissue must be received by the central vendor in order to randomize a subject to study treatment.<br><br><u>Key Exclusion Criteria:</u><br>• Any history of or current central nervous system (CNS) metastases. Baseline imaging of the brain is required within 28 days prior to randomization<br>• Prior systemic treatment with VEGF or VEGF receptor targeted therapy | Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV infusion every 3 weeks for 4 doses then Nivolumab 3 mg/kg IV every 2 weeks<br><br>Sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off, continuously | <u>Co-primary</u><br>• OS, PFS and ORR based on IRRC assessments in intermediate/poor risk subjects<br><br><u>Secondary</u><br>• ORR, PFS, OS in ITT population<br><br><u>Exploratory</u><br>• ORR, PFS, OS in favourable risk patients<br>• ORR, PFS, OS according to level of PD-L1 expression |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| N enrolled = 1082<br><br>Patient Enrolment Dates: From October 2014 through February 2016<br><br>Database lock: 07 August, 2017<br><br>June 26, 2017 (Final data collection date for primary outcome measure)<br><br>Estimated completion date: September 30, 2019<br><br>Sponsor: Bristol-Myers Squibb | (including, but not limited to, Sunitinib, Pazopanib, Axitinib, Tivozanib, and Bevacizumab)<br>• Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways<br>• Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (>10 mg daily Prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll<br>• Any condition requiring systemic treatment with corticosteroids (>10 mg daily Prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily Prednisone equivalents are permitted in the absence of active autoimmune disease | | |

AE= Adverse event; DOR= Duration of response; ITT= Intent to treat; mRCC= Metastatic renal cell carcinoma; PFS=

Progression-free survival; ORR= Objective response rate; OS= Overall survival, PD-1 = Programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PD-L2 = Programmed death-ligand 2; CD137 = cluster of differentiation 137; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IRRC = independent radiology review committee

Sources: clinicaltrials.gov, NCT01472081; CheckMate 214[2]

**[Table 5]: Select quality characteristics of the included trial[2] of nivolumab plus ipilimumab in patients with previously untreated advanced/metastatic RCC**

| Study | Treatment vs. comparator | Primary outcome | Required sample size | Sample size | Randomization method | Allocation concealment | Blinding | ITT analysis | Final analysis | Early termination | Ethics approval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CheckMate 024 | Nivolumab Plus Ipilimumab vs. Sunitinib | PFS, OS, ORR | 1070 | 1,096 | NR | No | No | Yes | Yes* | Yes* | Yes |

*The cut-off for this analysis was August 7, 2017, after which the independent Data Monitoring Committee recommended stopping the trial at the first planned interim analysis on September 6th, 2017 for reasons of statistical superiority

## PIVOTAL TRIAL – CHECKMATE 214

### *a) Trials*

CheckMate 214 was a phase III, randomized, open-label trial of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy for previously untreated clear-cell advanced renal-cell carcinoma (RCC). Randomization was performed in a 1:1 ratio with a block size of 4 with stratification according to IMDC risk score (0, 1 or 2, 3 to 6) and geographic region (United States, Canada and Europe, the rest of the world).

A November 2017 protocol amendment, after the primary end point had been met, permitted crossover from the sunitinib group to the nivolumab-plus-ipilimumab group. Nivolumab, ipilimumab, and sunitinib were provided by the sponsors, except when sunitinib was procured as a local commercial product in certain countries.

Between October 2014 and February 2016, 1096 eligible adult patients with previously untreated advanced or metastatic RCC patients were randomized, and of those 1082 received treatment. The study included adults (>18 years) with advanced (either not amenable to curative surgery or radiation, or AJCC Stage IV) histologically confirmed RCC with a clear-cell component. Prior systemic therapy for RCC was not permitted except for one prior adjuvant or neoadjuvant therapy provided such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. Subjects were to have a Karnofsky Performance Status (KPS) of at least 70%. To be eligible for the intermediate/poor-risk cohort, at least 1 of the 6 following prognostic factors as per IMDC criteria had to be present: 1) KPS equal to 70%; 2) less than year from diagnosis to randomization; 3) hemoglobin < lower limit of normal; 4) corrected calcium concentration > 10 mg/dL; 5) absolute neutrophil count > upper limit of normal; 6) platelet count > ULN.

The co-primary end points were the objective response rate, progression-free survival, and overall survival among intermediate- and poor-risk patients. Secondary end points included the objective response rate, progression-free survival, and overall survival, all in the intention-to-treat population; and the incidence rate of adverse events among all treated patients. Exploratory end points included the objective response rate, progression free survival, and overall survival, all among favorable-risk patients. Additional exploratory end points included outcomes according to the level of tumor programmed death ligand 1 (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, and health-related quality of life on the basis of the score on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19), both in intermediate- and poor-risk patients.

Disease assessments were performed with computed tomography or magnetic resonance imaging at baseline, 12 weeks after randomization, continuing every 6 weeks for the first 13 months, and then every 12 weeks until progression or

treatment discontinuation. After progression or treatment discontinuation, patients were followed for safety and survival. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients in both groups were allowed to continue therapy after initial investigator-assessed, RECIST-defined progression if they had clinical benefit without disabling toxic effects. Patients discontinued trial therapy on evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions) according to investigator assessment.

The sample size of the study accounted for the three co-primary efficacy end points: ORR and PFS as per Independent Radiology Review Committee (IRRC), and OS evaluated in intermediate and poor-risk subjects with previously untreated mRCC. The overall alpha for this study was 0.05, which was split into 0.001 for ORR, 0.009 for PFS, and 0.04 for OS. This study was powered to approximately 80% for PFS analysis and 90% for OS analysis, to determine statistically significant differences between treatment arms. Overall survival was evaluated on the basis of a hazard ratio of 0.77, accounting for two formal interim analyses after 51% and 75% of deaths had occurred, using a stratified log-rank test. It was estimated that 1070 patients would undergo randomization, 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). Enrollment was discontinued once approximately 820 patients (77%) with IMDC intermediate or poor risk had undergone randomization.

### *b) Populations*

Details for baseline characteristics for CheckMate 214 are listed in Table 6. There were a total of 1096 eligible patients randomized into the study (547 in the nivolumab plus ipilimumab arm and 535 in the sunitinib arm in the intention-to-treat population; 423 and 416, respectively, had intermediate or poor risk). The groups were well-balanced with respect to demographic characteristics. The vast majority (>71%) of patients were male and there was an overall median age of 61-62 years in both treatment groups (Table 6). A total of 79% patients had a prognostic score of 1–2 (intermediate-risk) while the remaining 21% were within the poor-risk category (Table 6). Approximately a quarter of all patients were enrolled from the United States, with approximately 35% enrolled from Canada or Europe and 39% enrolled from other parts of the world. Greater than 75% of all patients had previous nephrectomy, but less than 13% of all patients had previous radiotherapy. Metastases most often occurred in the lungs, followed by lymph node, bones and liver.

Of the intermediate/poor-risk subjects who had a baseline tumor tissue sample tested for PD-L1, 100/384 (26%) in the nivolumab + ipilimumab group and 114/392 (29%) in the sunitinib group had tumors that were positive for PD-L1 expression (≥1%) at baseline.

Among intermediate/poor-risk subjects, most (99.3% and 99.5%) subjects in the nivolumab + ipilimumab and sunitinib groups, respectively, had received no prior anticancer therapy.[8] A total of 0.5% of subjects in the nivolumab + ipilimumab and

sunitinib groups, respectively, received prior systemic therapy in the adjuvant setting and 0.2% of subjects in the nivolumab + ipilimumab and no sunitinib subjects received prior systemic therapy in the neoadjuvant setting. The most frequent prior systemic cancer therapies in the nivolumab + ipilimumab and sunitinib groups were interferon and interferon alpha (0.2%) for both treatment groups and interleukin 1 (0.2%) in the nivolumab + ipilimumab group.[8]

**Table 6. Baseline Characteristics and Clinical Characteristics of the Patients Who Underwent Randomization* in CheckMate 214[2]**

| Characteristic | IMDC Intermediate- and Poor-Risk Patients | | Intention-to-Treat Population | |
|---|---|---|---|---|
| | Nivolumab plus Ipilimumab (N=425) | Sunitinib (N=422) | Nivolumab plus Ipilimumab (N=550) | Sunitinib (N=546) |
| Median age (range) — yr | 62 (26–85) | 61 (21–85) | 62 (26–85) | 62 (21–85) |
| Sex — no. (%) | | | | |
| Male | 314 (74) | 301 (71) | 413 (75) | 395 (72) |
| Female | 111 (26) | 121 (29) | 137 (25) | 151 (28) |
| IMDC prognostic risk — no. (%)† | | | | |
| Favorable | 0 | 0 | 125 (23) | 124 (23) |
| Intermediate | 334 (79) | 333 (79) | 334 (61) | 333 (61) |
| Poor | 91 (21) | 89 (21) | 91 (17) | 89 (16) |
| Geographic region — no. (%) | | | | |
| United States | 112 (26) | 111 (26) | 154 (28) | 153 (28) |
| Canada and Europe | 148 (35) | 146 (35) | 201 (37) | 199 (36) |
| Rest of the world | 165 (39) | 165 (39) | 195 (35) | 194 (36) |
| Quantifiable tumor PD-L1 expression — no./ total no. with evaluable data (%) | | | | |
| <1% | 284/384 (74) | 278/392 (71) | 386/499 (77) | 376/503 (75) |
| ≥1% | 100/384 (26) | 114/392 (29) | 113/499 (23) | 127/503 (25) |
| Previous radiotherapy — no. (%) | 52 (12) | 52 (12) | 63 (11) | 70 (13) |
| Previous nephrectomy — no. (%) | 341 (80) | 319 (76) | 453 (82) | 437 (80) |
| No. of sites with target or nontarget lesions — no. (%)‡ | | | | |
| 1 | 90 (21) | 84 (20) | 123 (22) | 118 (22) |
| ≥2 | 335 (79) | 337 (80) | 427 (78) | 427 (78) |
| Most common sites of metastasis — no. (%) | | | | |
| Lung | 294 (69) | 296 (70) | 381 (69) | 373 (68) |
| Lymph node | 190 (45) | 216 (51) | 246 (45) | 268 (49) |
| Bone§ | 95 (22) | 97 (23) | 112 (20) | 119 (22) |
| Liver | 88 (21) | 89 (21) | 99 (18) | 107 (20) |

* Information shown in the table is based on data collected with the use of an interactive voice-response system. Percentages may not total 100 because of rounding. IMDC denotes International Metastatic Renal Cell Carcinoma Database Consortium, and PD-L1 programmed death ligand 1.

† Patients with favorable risk had an IMDC score of 0, those with intermediate risk had a score of 1 or 2, and those with poor risk had a score of 3 to 6. IMDC risk scores are defined by the number of the following risk factors present: a Karnofsky performance-status score of 70 (on a scale from 0 to 100, with lower scores indicating greater disability; patients with a performance-status score of <70 were excluded from the trial), a time from initial diagnosis to randomization of less than 1 year, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium concentration of more than 10 mg per deciliter (2.5 mmol per liter), an absolute neutrophil count above the upper limit of the normal range, and a platelet count above the upper limit of the normal range.

‡ The number of target or nontarget lesions at baseline was not reported for one patient in the sunitinib group.

§ Shown are patients who had bone metastases with or without a soft-tissue component.

From The New England Journal of Medicine, Motzer RJ, Tannir NM, McDermott DR, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, Volume 378, Page 1281. Copyright © 2018. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

### *c) Intervention*

Patients received nivolumab and ipilimumab intravenously at a dose of 3 mg per kilogram over a period of 60 minutes and 1 mg per kilogram, respectively over a period of 30 minutes, respectively, every 3 weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg per kilogram every 2 weeks (maintenance phase). Sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of each 6-week cycle. Treatment was continued until RECIST 1.1 defined progression or unacceptable toxicity. Subjects were allowed to continue study therapy after initial investigator-assessed RECIST v1.1-defined progression if the subject had an investigator-assessed clinical benefit and was tolerating study drug. No dose reductions were allowed for nivolumab or ipilimumab. Dose delays for adverse events were permitted in both groups. Patients treated with nivolumab plus ipilimumab had to discontinue both nivolumab and ipilimumab if they had a treatment-related adverse event during the induction phase that necessitated discontinuation, and they could not continue on to nivolumab maintenance therapy, irrespective of the attribution of the adverse event. In the sunitinib arm, patients were required to permanently discontinue sunitinib if more than two sunitinib dose reductions occurred.

Based on the Health Canada product monograph for nivolumab, the recommended dose for nivolumab is 3mg/kg over 30 minutes every 3 weeks for the first 4 doses when combined with ipilimumab and 3mg/kg iv over 30 minutes every 2 weeks or 240mg every 2 weeks or 480 mg every 4 weeks over 30 minutes when administered as a single agent. The product monograph indicates that there are no clinically significant differences in safety and efficacy between a nivolumab dose of 240 mg every 2 weeks or 480 mg every 4 weeks or 3 mg/kg every 2 weeks. There was no information on whether or not nivolumab can be administered at 6mg/kg up to a maximum of 480mg every 4 weeks.[31]

### *d) Patient Disposition*

For all treated patients the median follow-up was 25.2 months; the minimum

follow-up was 17.5 months. The median duration of treatment was 7.9 months in the nivolumab + ipilimumab group and 7.8 months in the sunitinib group (Table 7).

A total of 79% of patients received all four doses of ipilimumab with nivolumab. Among the 547 patients treated with nivolumab plus ipilimumab, nivolumab dose delays occurred in 319 (58%), and ipilimumab dose delays occurred in 148 (27%). Among the 535 patients treated with sunitinib, dose delays occurred in 315 (59%), and dose reductions occurred in 283 (53%). A total of 157 of 550 patients (29%) in the nivolumab plus-ipilimumab arm and 129 of 546 patients (24%) in the sunitinib group were treated beyond initial investigator-assessed, RECIST-defined progression, as permitted according to the protocol.

Across all treated patients, treatment discontinuation was slightly higher in the sunitinib arm than in the nivolumab + ipilimumab treated arm. Of those that received treatment, treatment was discontinued by 419 subjects (76.6%) in the nivolumab + ipilimumab arm and 438 (81.9%) in the sunitinib arm. In both groups, the most common reasons for discontinuation were disease progression (41.9% vs. 55.3%, respectively), and study drug toxicity (24.5% vs. 11.8%, respectively; (Table 7). Disease progression was the most common cause of death for both groups. Seven (1.3%) treatment-related deaths were reported in the nivolumab + ipilimumab group vs. four (0.7%) in the sunitinib group.[8]

**Table 7: Patient Disposition for All Treated Patients in CheckMate 214[2,5]**

| Characteristic | Nivolumab + Ipilimumab N = 547 | Sunitinib N = 535 |
|---|---|---|
| Treatment discontinuation, n (%) | 419 (77) | 438 (82) |
| Reasons for treatment discontinuation, n (%) | | |
| Disease progression | 229 (42) | 296 (55) |
| Study drug toxicity | 134 (24) | 63 (12) |
| Adverse event unrelated to study drug | 32 (6) | 31 (6) |
| Median duration of therapy (95% CI), months | 7.9 (6.5–8.4). | 7.8 (6.4–8.5) |
| Median doses received (range), no. | | |
| Nivolumab | 14 (1–63) | NA |
| Ipilimumab | 4 (1–4) | NA |
| Sunitinib | NA | NA 154.0 (1-838) |
| Median daily dose (range), mg/day | NA | 31 (14–50) |
| Infusion Interruptions (N+I)[b] or dose reductions (S)[c], % | | |
| Nivolumab | 5 | NA |
| Ipilimumab | 1 | NA |
| Sunitinib | NA | 53 |
| Patients with ≥1 dose delay, %[d] | | |
| Nivolumab | 58 | NA |
| Ipilimumab | 27 | NA |
| Sunitinib | NA | 59 |

[a]Other includes subjects request to discontinue study treatment, withdrawal of consent, lost to follow-up, maximum clinical benefit, poor/noncompliance, pregnancy[8]
[b]infusion interruption was defined as when the intravenous infusion was stopped during the infusion period (it may have been restarted or not)
[c] Dose reductions were not permitted with N+I treatment
[d]Dose delay was defined as a delay in the start of a new cycle (beyond any study defined window) or the next dose within a cycle (if so designated and, again, outside a window)
NA= Not applicable
**Source**: Motzer et al., 2018[2]; Tannir Risk Benefit poster[5]

### *e) Limitations/Sources of Bias*

Overall, CheckMate 214 was a well-designed phase III RCT. However, the trial used an open-label design, making the investigators, other study personnel and participants aware of the treatment allocation (Table 5). The rationale for an open-label methodology was based on multiple factors, including different routes of administration (intravenous for nivolumab + ipilimumab versus oral for sunitinib), different treatment schedules (every three weeks for four doses for nivolumab + ipilimumab, then nivolumab every 2 weeks versus daily for 4 weeks for sunitinib), different dose modification rules, different safety profiles and different management of AEs between the two study groups. Although the primary endpoints of the study, OS, ORR, and PFS are objective outcomes or objectively assessed, an open-label study design could have introduced some levels of bias to the investigator's assessment of PFS and ORR, patient-reported outcomes, as well as assessment and reporting of drug-related AEs. Furthermore, assessment of HRQoL outcomes were exploratory and the clinical significance of the results remain uncertain.

## 6.3.2.2 Detailed Outcome Data and Summary of Outcomes[2]

**CHECKMATE 214**

***Efficacy Outcomes***

The results presented for this section from CheckMate 214 are for patients within the intermediate/poor-risk groups to reflect the expected indication for the nivolumab + ipilimumab combination. The cut-off for this analysis was August 2017, after which the independent Data Monitoring Committee (DMC) recommended stopping the trial at the first interim analysis on September 6th, 2017 for reasons of statistical superiority.

**CO-PRIMARY OUTCOMES**

**Overall Survival (OS) in IMDC Intermediate/Poor-Risk Subjects**

Nivolumab plus ipilimumab had a significant overall survival benefit compared to sunitinib; the 12-month overall survival rate was 80% (95% CI, 76 to 84) with nivolumab plus ipilimumab versus 72% (95% CI, 67 to 76) with sunitinib, and the 18-month overall survival rate was 75% (95% CI, 70 to 78) versus 60% (95% CI, 55 to 65). The between-group difference met the prespecified threshold for statistical significance at an adjusted alpha level of 0.002 for first interim analysis (hazard ratio for death, 0.63; 99.8% CI, 0.44 to 0.89; P<0.001) (Table 8). The median overall survival was not reached (95% CI, 28.2 months to not estimable) with nivolumab plus ipilimumab versus 26.0 months (95% CI, 22.1 to not estimable) with sunitinib. Nivolumab + ipilimumab provides a statistically significant OS gain over sunitinib and a 37% reduction in the risk of death in patients with previously untreated advanced or metastatic RCC in the intermediate/poor-risk group.

In the intermediate/poor-risk group, categorized according to IMDC, statistically significant OS gains were observed for nivolumab + ipilimumab compared with sunitinib regardless of the PD-L1 expression. At 12 months, the probability of OS was 80% (95% CI, 75 to 84) in patients being treated with nivolumab + ipilimumab compared to 75% (95% CI, 70 to 80) with sunitinib in patients who had low (<1%) PD-L1 expression. 18-month overall survival rate was 74% (95% CI, 69 to 79) and 64% (95% CI, 58 to 70), respectively; the median overall survival was not reached in both groups (hazard ratio for death, 0.73; 95% CI, 0.56 to 0.96). In patients with 1% or greater PD-L1 expression, the 12-month overall survival rate was 86% (95% CI, 77 to 91) with nivolumab plus ipilimumab and 66% (95% CI, 56 to 74) with sunitinib, and the 18-month overall survival rate was 81% (95% CI, 71 to 87) and 53% (95% CI, 43 to 62), respectively; the median overall survival was not reached and 19.6 months (95% CI, 14.8 to not estimable), respectively (hazard ratio for death, 0.45; 95% CI, 0.29 to 0.71).

**Progression-Free Survival (PFS) per IRRC in IMDC Intermediate/Poor-Risk Subjects**
The interim analysis showed that the median PFS was 11.6 months (95% CI, 8.7 to 15.5) for nivolumab + ipilimumab, compared with 8.4 months (95% CI, 7.0 to 10.8 for sunitinib (Table 8). The between-group difference did not meet the prespecified threshold (P = 0.009) for statistical significance (hazard ratio for disease progression or death, 0.82; 99.1% CI, 0.64 to 1.05; P = 0.03). Although not statistically significant, median PFS with nivolumab + ipilimumab was more than 3 months longer than with sunitinib.

The Kaplan-Meier curves, presented as Figure 2 in Motzer et al, (ref=Motzer 2018) overlapped until approximately six months and then separated, favouring nivolumab + ipilimumab beyond this time point; the effect was more pronounced over time when looking at the tail of the curve.

**Objective Response Rate (ORR) in IMDC Intermediate/Poor-Risk Subjects**
The combination of nivolumab + ipilimumab was associated with a significantly higher ORR than sunitinib, as assessed by IRRC, with 42% (95% CI, 37 to 47) of patients achieving ORR criteria in the nivolumab + ipilimumab group vs. 27% in the sunitinib group (95% CI, 22 to 31; *P*< 0.001; Table 8). A significantly higher proportion of subjects achieved a CR in the nivolumab + ipilimumab group compared to the sunitinib group (9% vs. 1%, respectively, *P*< 0.001).

**Secondary Endpoints**
In the all randomized population, treatment with nivolumab + ipilimumab demonstrated statistically longer OS compared with sunitinib, which included favorable-, intermediate-, and poor-risk subjects, at the planned interim OS analysis (HR: 0.68 [99.8% CI: 0.49 to 0.95]; stratified log-rank test 2-sided p-value < 0.001; Table 8) at the adjusted alpha of 0.002.

Treatment with nivolumab + ipilimumab combination therapy demonstrated a higher ORR in the all randomized population, which included favorable-, intermediate-, and poor-risk subjects: nivolumab + ipilimumab group: 38.7% (95% CI: 34.6, 42.9) vs sunitinib group: 32.2% (95% CI: 28.3, 36.3), with a difference in

ORR of 7.2% (95% CI: 1.8, 12.7), p = 0.0191. A total of 9.8% vs 2.2% of subjects achieved a CR in the nivolumab + ipilimumab and sunitinib groups, respectively.

Responses in the nivolumab + ipilimumab group occurred early in the all randomized populations (median TTR was 2.79 months) and were durable (median DOR was not reached at the time of database lock). In the sunitinib group, median time to response was similar but responses were less durable.

PFS analysis assessed by IRRC was only for qualitative purposes due to hierarchical testing. PFS observed in all randomized subjects, including favorable-risk subjects, showed HR=0.98, 99.1% CI: 0.79-1.23, stratified log-rank 2-sided p=0.8498 in the nivolumab + ipilimumab group vs the sunitinib group. The median PFS was 12.42 months for nivolumab + ipilimumab and 12.32 months for sunitinib.

**Duration of Response**

The interim analysis of the CheckMate 214 data showed a trend towards an increased DOR in intermediate- and poor-risk patients who received nivolumab + ipilimumab. The median DOR was not reached, however the minimum DOR was 21.8 months for patients treated with nivolumab + ipilimumab, whereas those treated with sunitinib demonstrated a median duration of response of 18.2 months (Table 8).

**Time to Response and Duration of Response per IRRC**

In intermediate/poor-risk subjects, responses in the nivolumab + ipilimumab group occurred early (median TTR of 2.8 months) and were durable (median DOR was not reached at the time of database lock, 95% CI 21.8-NE). In the sunitinib group, median time to response was similar (3.0 months, 95% CI 0.6-15.0) but responses were less durable (median DOR 18.2 months, 95% CI 14.8-NR).

**Table 8: Summary of Key Efficacy Outcomes in CheckMate 214 trial[2]**

| Antitumor Activity in IMDC Intermediate- and Poor-Risk Patients.* | | |
|---|---|---|
| **Variable** | **Nivolumab plus Ipilimumab (N = 425)** | **Sunitinib (N = 422)** |
| Confirmed objective response rate — % (95% CI)† | 42 (37–47)‡ | 27 (22–31)‡ |
| Confirmed best overall response — no. (%)† | | |
| Complete response | 40 (9)‡§ | 5 (1)‡§ |
| Partial response | 137 (32) | 107 (25) |
| Stable disease | 133 (31) | 188 (45) |
| Progressive disease | 83 (20) | 72 (17) |
| Unable to determine or not reported | 32 (8) | 50 (12) |
| Median time to response (range) — mo | 2.8 (0.9–11.3) | 3.0 (0.6–15.0) |
| Median duration of response (95% CI) — mo | NR (21.8–NE) | 18.2 (14.8–NE) |
| Patients with ongoing response — no./total no. (%) | 128/177 (72) | 71/112 (63) |

* NE denotes not estimable, and NR not reached.

† Response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent radiology review committee.

‡ P<0.001 for the difference between groups.

§ The analysis of the between-group difference in complete response was exploratory.

From The New England Journal of Medicine, Motzer RJ, Tannir NM, McDermott DR, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, Volume 378, Page 1283. Copyright © 2018. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

**Subsequent Therapy**

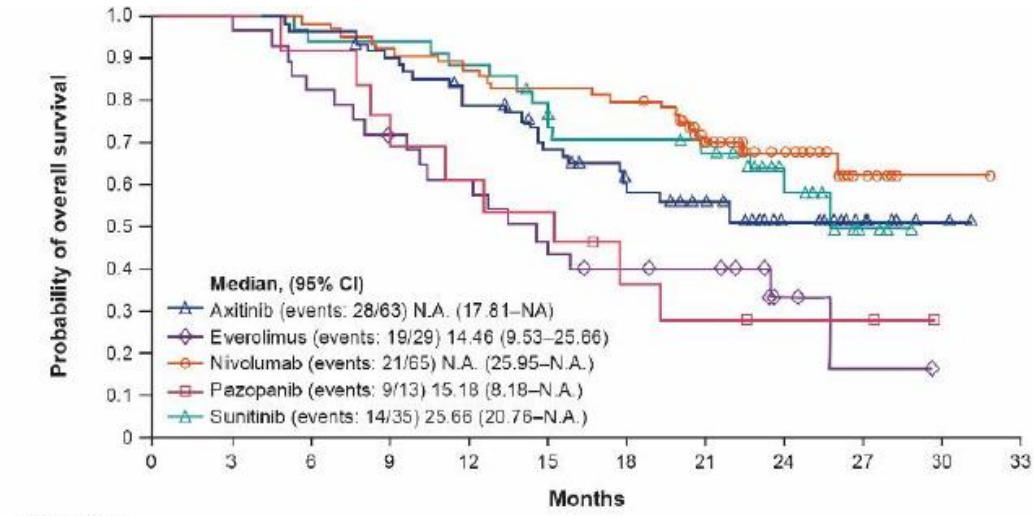
Among all randomly assigned patients, 217 of 550 (39%) in the nivolumab+ ipilimumab group and 295 of 546 (54%) in the sunitinib group received subsequent systemic therapy. The most common subsequent therapies were sunitinib (111 patients, 20%) and pazopanib (72 patients, 13%) in the nivolumab-plus-ipilimumab group and nivolumab (147 patients, 27%) and axitinib (106 patients, 19%) in the sunitinib group.

A total of 28.5% (157/550) of treated subjects in the nivolumab + ipilimumab group and 23.6% (129/546) of treated subjects in the sunitinib group were treated beyond progression (defined as a last dosing date after investigator-assessed RECIST v1.1 progression date). The duration of time patients continued on assigned treatment varied for each individual and continued as long as investigator-assessed clinical benefit was achieved and treatment was well tolerated. Patients discontinue study

therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions) according to investigator assessment.[20,30]

The survival curves showed that for the sunitinib arm (Figure 2A), patients receiving nivolumab as a subsequent therapy had a higher OS after sunitinib, while for the nivolumab + ipilimumab arm patients receiving axitinib had a higher OS (Figure 2B).[8]

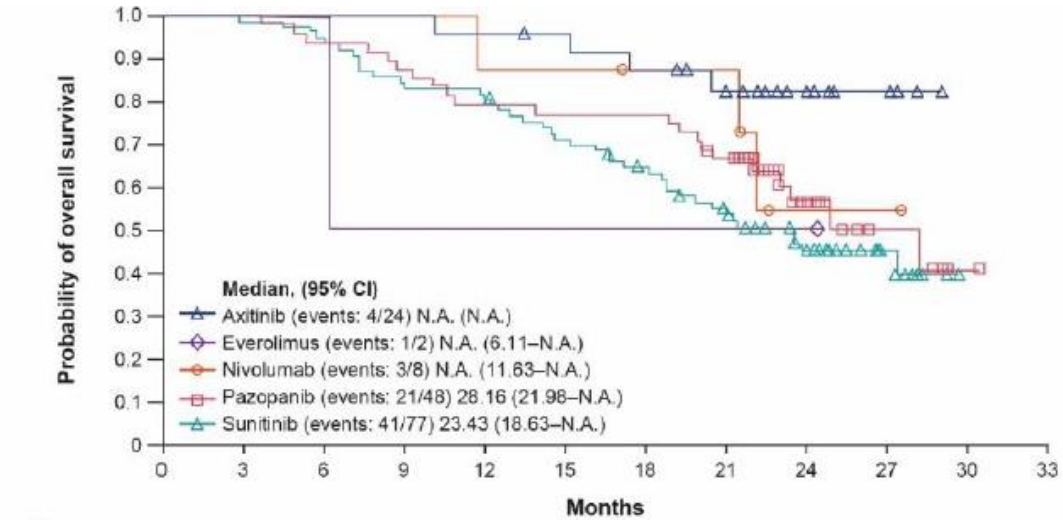
**FIGURE 2A Survival by Subsequent Treatment – Sunitinib[8]**




| No. at risk: | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Axitinib | 63 | 63 | 61 | 56 | 48 | 40 | 31 | 25 | 14 | 7 | 2 | 0 |
| Everolimus | 29 | 28 | 24 | 20 | 17 | 12 | 10 | 9 | 3 | 1 | 0 | 0 |
| Nivolumab | 65 | 65 | 64 | 60 | 57 | 54 | 52 | 37 | 22 | 8 | 1 | 0 |
| Pazopanib | 13 | 13 | 12 | 9 | 8 | 7 | 4 | 3 | 2 | 2 | 0 | 0 |
| Sunitinib | 35 | 35 | 33 | 33 | 31 | 25 | 23 | 21 | 10 | 3 | 0 | 0 |

N.A.= Not available
Source: BMS Data on File, Confidential Data[104]

**FIGURE 2B: Survival by Subsequent Treatment – Nivolumab + Ipilimumab[8]**




| No. at risk: | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Axitinib | 24 | 24 | 24 | 24 | 23 | 22 | 20 | 16 | 10 | 5 | 0 | 0 |
| Everolimus | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| Nivolumab | 8 | 8 | 8 | 8 | 7 | 7 | 6 | 6 | 2 | 2 | 0 | 0 |
| Pazopanib | 48 | 48 | 45 | 42 | 38 | 37 | 37 | 31 | 14 | 5 | 1 | 0 |
| Sunitinib | 77 | 76 | 73 | 64 | 62 | 54 | 47 | 38 | 24 | 8 | 0 | 0 |

N.A.= Not available
Source: BMS Data on File, Confidential Data[104]

### *Health-related Quality of Life[2-4]*

The exploratory outcome of patient-reported disease related symptoms was assessed using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19) in intermediate- and poor-risk patients. General health status was assessed using the EuroQol EQ-5D, Health Related Quality of Life (HRQoL) was assessed by the Functional Assessment of Cancer Therapy-General (FACT-G).[4] Total FKSI-19 scores range from 0 to 76, total FACT-G scores range from 0-108 and EQ-5D ranges from 0-1 for the utility index and 0-100 for the VAS index. For all measurements, numerically higher scores indicate fewer symptoms and a more favourable outcome.[4] All HRQoL analyses are descriptive in nature, with *t*-tests or unstratified log-rank tests used to evaluate between-group difference in mean change from baseline. A pattern-mixture model and a restricted maximum likelihood–based repeated-measures approach were then used to confirm descriptive data. However, additional analyses are needed to elucidate the clinical importance of HRQoL as a potential factor influencing survival.

With completion rates of the FKSI-19 questionnaire exceeding 80% during the first 6 months, significant differences in mean change from baseline was greater in the nivolumab + ipilimumab group compared to the sunitinib group for all assessments during the first 6 months ($p<0.001$) and were sustained at all but two post-baseline time points through two years of follow-up ($p<0.05$) (Figure 2A).[4] ( The mean

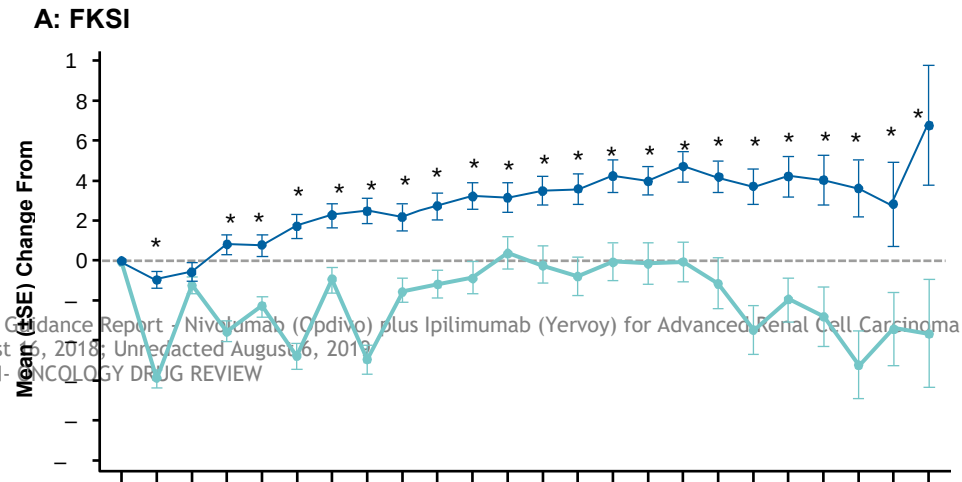
change from baseline in FACT-G total score was significantly improved compared with sunitinib at approximately half of the assessment time points (Figure 2B).[3] (Cella ASCO 2018 slides). Mean EQ-5D VAS scores increased over time with both nivolumab + ipilimumab and sunitinib; differences between treatment arms were not statistically significant (Figure 2C).[3] If and how these statistically significant differences translate to clinically meaningful changes for patients was not discussed.

Time to deterioration (TTD) in FKSI-19 total score (defined as the first decrease of ≥3 points) was significantly delayed with nivolumab + ipilimumab versus sunitinib (HR 0.54; 95% CI, 0.46–0.63; *P* < 0.0001) with a median TTD of 2.2 months versus 1.0 months for nivolumab + ipilimumab versus sunitinib.[3] TTD was also significantly delayed with nivolumab + ipilimumab versus sunitinib in both FACT-G total (HR 0.63; 95% CI, 0.52–0.75; *P* < 0.0001) and EQ-5D VAS (HR 0.75; 95% CI, 0.63–0.89; *P* = 0.0016) scores, both defined as the first decrease of ≥7 points.[3]

Mixed effect model repeat measurement (MMRM) analysis (to assess changes from baseline in HRQoL scores at a 6-month (25 week) landmark) was conducted for the FKSI-19 analysis. This analysis controlled for baseline score and randomization factors, eg, IMDC prognostic score (0 vs 1–2 vs 3–6) and region (United States vs Canada/Europe vs the rest of the world). Results of this analysis showed that the difference between nivolumab + ipilimumab group compared to the sunitinib group in total was 2.63 (95% CI 1.13-4.13) (p<0.05). For disease-related symptoms, the difference was 0.75 (0.10-1.40) and for physical disease related symptoms the difference observed was 1.19 (0.28-2.11) (p<0.05 for both). Differences were also significant in favor of nivolumab + ipilimumab for the EQ-5D utility index and VAS scores.[3]

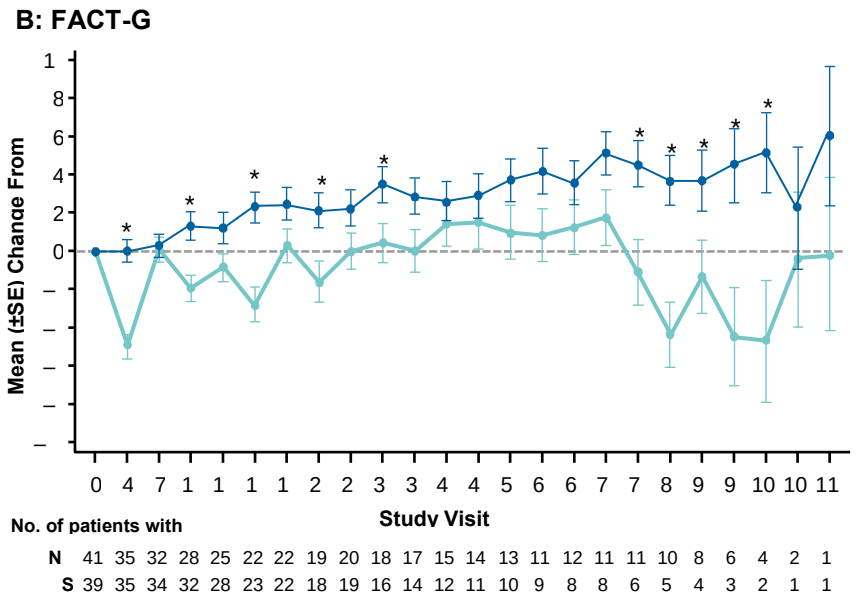
[redacted]. (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*). In fact, across all 3 patient-reported scales, the nivolumab + ipilimumab group reported numerically higher scores compared to baseline scores and compared to the sunitinib group.[8]

**Figure 3A. Change from baseline in mean FKSI scores over time in intermediate/poor-risk patients (descriptive analyses)** [3]



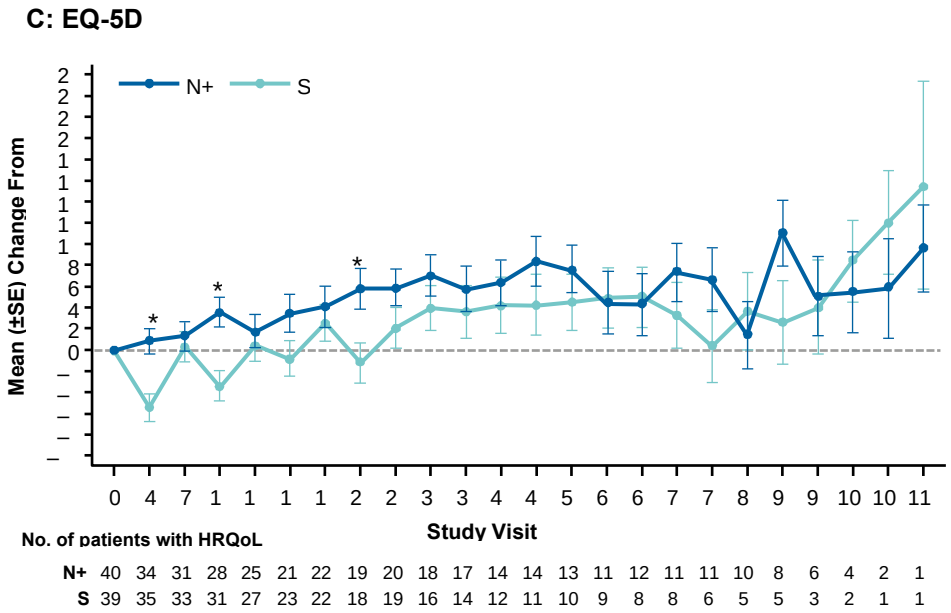
Includes only patients with evaluable HRQoL assessments
*denotes significant differences in mean change from baseline between treatment arms ($P < 0.05$)
SE = standard error

**Figure 3B. Change from baseline in mean FACT-G scores over time in intermediate/poor-risk patients (descriptive analyses)[3]**




Includes only patients with evaluable HRQoL assessments
*denotes significant differences in mean change from baseline between treatment arms ($P < 0.05$)
SE = standard error

**Figure 3C. Change from baseline in mean EQ-5D scores over time in intermediate/poor-risk patients (descriptive analyses).[3]**




Includes only patients with evaluable HRQoL assessments
*denotes significant difference in mean change from baseline between treatment arms ($P < 0.05$)

## Harms Outcomes[2,5]

### Treatment-Related Adverse Events

Safety analyses were conducted in all 1082 treated subjects who received at least 1 dose of study drug. The all-treated population was the primary population for safety analyses to maximize the size of the safety database. In the all-treated population, 93% and 97% of subjects reported at least one treatment-related AE in the nivolumab + ipilimumab and sunitinib groups, respectively (Table 9). The proportion of grade ≥3 was lower in the nivolumab + ipilimumab group (46%) compared to the sunitinib group (63%). Safety analyses for the intermediate/poor risk population were consistent with the all treated population.

The most common AEs (any grade) in the nivolumab + ipilimumab group were fatigue (37%), pruritus (28%) and diarrhea (27%), whereas in the sunitinib group the most common events were diarrhea (52%), fatigue (49%) and palmar-plantar erythrodysesthesia syndrome (43%). Reporting of hypertension was 40% in the sunitinib group (16% with grade 3 or 4) compared to 2% (< 1% with grade 3 or 4) in the nivolumab + ipilimumab group.

Any-grade treatment-related select AEs resolved in 72-92% of patients receiving nivolumab + ipilimumab and in 67-100% of patients receiving sunitinib, with the exception of endocrinopathies (43% and 37%,respectively) which required permanent hormone replacement.[5] Among patients treated with nivolumab plus ipilimumab, 436 had immune-mediated adverse events that included skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories. Of these, 152 (35%) received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent). Concomitant immune-modulating medications (IMMs) were administered for management of AEs in 72% of patients in the nivolumab plus ipilimumab arm and 33% of patients in the sunitinib arm. IMM included systemic corticosteroids in 60% and 17% of patients, respectively. Secondary immunosuppression with infliximab (2%) and mycophenolic acid (1%) was also required in patients treated with nivolumab plus ipilimumab. There was no data available on the occurrence of imAE's in the sunitinib group.

**Table 9: Summary of Safety Results - All Treated Subjects in CheckMate 214[2,5,6,8]**

**A: Selected Harms outcomes**

| | Nivolumab + Ipilimumab, n=547 | | Sunitinib, n=535 | |
|---|---|---|---|---|
| Deaths | 159 (29.1) | | 202 (37.8) | |
| Within 30 days of last dose | 23 (4.2) | | 25 (4.7) | |
| Within 100 days of last dose | 50 (9.1) | | 77 (14.4) | |
| Due to study drug toxicity | 7 (1) | | 4 (1) | |
| | Nivolumab + Ipilimumab, n=547 | | Sunitinib, n=535 | |
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| All causality SAE's | 305 (55.8) | 227 ( 41.5) | 213 ( 39.8) | 161 ( 30.1) |
| Drug-related SAE's | 162 (29.6) | 121 ( 22.1) | 81 ( 15.1) | 64 ( 12.0) |
| All causality AE's leading to discontinuation | 168 (30.7) | 118 ( 21.6) | 114 ( 21.3) | 74 ( 13.8) |
| Drug-related AE's leading to discontinuation | 118 ( 21.6) | 84 (15.4%) | 63 (11.8%) | 37 (6.9%) |
| **Most frequent AEs (≥20% of any grade in either treatment group)** | | | | |
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| All causality AE's | 544 ( 99.5) | 357 ( 65.3) | 532 ( 99.4) | 407 ( 76.1) |
| Fatigue | 246 (45.0) | 34 (6.2) | 291 ( 54.4) | 54 ( 10.1) |
| Diarrhea | 205 ( 37.5) | 25 (4.6) | 310 ( 57.9) | 33 (6.2) |
| Purities | 180 (32.9) | 3 (0.5) | 58 (10.8) | 0 |
| Nausea | 163 ( 29.8) | 11 (2.0) | 230 ( 43.0) | 8 (1.5) |
| Cough | 145 ( 26.5) | 1 (0.2) | 125 ( 23.4) | 2 (0.4) |
| Rash | 141 ( 25.8) | 8 (1.5) | 84 ( 15.7) | 0 |
| Pyrexia | 136 ( 24.9) | 4 (0.7) | 91 ( 17.0) | 3 (0.6) |
| Arthralgia | 123 ( 22.5) | 7 (1.3) | 83 ( 15.5) | 0 |
| Decreased appetite | 114 ( 20.8) | 10 (1.8) | 156 ( 29.2) | 5 (0.9) |
| Vomiting | 109 ( 19.9) | 5 (0.9) | 149 ( 27.9) | 11 (2.1) |
| Headache | 103 ( 18.8) | 5 (0.9) | 121 ( 22.6) | 5 (0.9) |
| Hypothyroidism | 96 ( 17.6) | 2 (0.4) | 145 ( 27.1) | 1 (0.2) |
| Anemia | 72 ( 13.2) | 20 (3.7) | 109 ( 20.4) | 32 (6.0) |
| Hypertension | 52 (9.5) | 18 (3.3) | 231 ( 43.2) | 94 (17.6) |
| Dysguesea | 40 (7.3) | 0 | 185 ( 34.6) | 1 (0.2) |
| Dysepsia | 29 (5.3) | 0 | 112 ( 20.9) | 1 (0.2) |
| Stomatitis | 29 (5.3) | 0 | 153 ( 28.6) | 14 (2.6) |
| Palmar-plantar erythrodysaesthesia syndrom | 9 (1.6) | 0 | 237 ( 44.3) | 50 (9.3) |

**B: Treatment-Related Adverse Events Occurring in 15% or More of Treated Patients in Either Group.***

| Event | Nivolumab plus Ipilimumab (N=547) | | Sunitinib (N=535) | |
|---|---|---|---|---|
| | Any Grade† | Grade 3 or 4 | Any Grade‡ | Grade 3 or 4 |
| | *number of patients (percent)* | | | |
| 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 |
| Diarrhea | 145 (27) | 21 (4) | 278 (52) | 28 (5) |
| Rash | 118 (22) | 8 (1) | 67 (13) | 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) |
| Anemia | 34 (6) | 2 (<1) | 83 (16) | 24 (4) |
| Dysgeusia | 31 (6) | 0 | 179 (33) | 1 (<1) |
| Stomatitis | 23 (4) | 0 | 149 (28) | 14 (3) |
| Dyspepsia | 15 (3) | 0 | 96 (18) | 0 |
| Mucosal inflammation | 13 (2) | 0 | 152 (28) | 14 (3) |
| Hypertension | 12 (2) | 4 (<1) | 216 (40) | 85 (16) |
| Palmar–plantar erythrodysesthesia | 5 (<1) | 0 | 231 (43) | 49 (9) |
| Thrombocytopenia | 2 (<1) | 0 | 95 (18) | 25 (5) |

* These events were considered by investigators to be related to treatment.
† There were eight treatment-related deaths in the nivolumab-plus-ipilimumab group: one each due to pneumonitis, pneumonia and aplastic anemia (the cause of death in this case was updated after the database lock to treatment-related), immune-mediated bronchitis, lower gastrointestinal hemorrhage, the hemophagocytic syndrome, sudden death, liver toxic effects, and lung infection.
‡ There were four treatment-related deaths in the sunitinib group: two due to cardiac arrest and one each due to heart failure and multiple organ failure.

From The New England Journal of Medicine, Motzer RJ, Tannir NM, McDermott DR, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, Volume 378, Page 1286. Copyright © 2018. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## 6.4 Ongoing Trials

Ongoing trials of nivolumab plus ipilimumab for the treatment of advanced or metastatic renal cell carcinoma below.

[Table 12]: Ongoing trials of nivolumab plus ipilimumab for the treatment of advanced or metastatic renal cell carcinoma

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| CheckMate 800<br><br>An Investigational Immuno-Therapy Safety and Efficacy Study of Multiple Administration Regimens for Nivolumab Plus Ipilimumab in Subjects With Renal Cell Carcinoma<br><br>NCT03029780<br><br>Phase II, Randomized, Open Label, Parallel Assignment<br><br>**N**: 118<br><br>Sponsor: Bristol-Myers Squibb<br><br>Start date: Feb 2017<br>End date Feb 2021 | Inclusion:<br>• Advanced Renal Cell Carcinoma<br>• Must have full activity or, if limited, must be able to walk and carry out light activities such as light house work or office work<br>• Must have at least 1 lesion with measurable disease<br><br>Exclusion Criteria:<br>• Subjects with active central nervous system metastases<br>• Subjects who received prior therapy with checkpoint inhibitor<br>• Subjects with active, known or suspected autoimmune disease | Nivolumab and Ipilimumab Co-Administration<br><br>Nivolumab and Ipilimumab Sequential Administration<br><br>Biological:<br>Specified dose on specified days of<br>Nivolumab<br><br>Specified dose on specified days<br>Of Ipilimumab | Primary:<br>AEs<br><br>Secondary:<br>AEs, ORR, PFS |
| Nivolumab vs Nivolumab + Bevacizumab vs Nivolumab + Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC)<br><br>NCT02210117<br><br>A Pilot, Phase I, Randomized, Open Label, Parallel Assignment<br><br>**N**: 106<br><br>Sponsor: Bristol-Myers Squibb<br><br>Start date: Nov 2014<br>End date Nov 2020 | Inclusion:<br>• Histologically or cytologically confirmed metastatic clear cell RCC who are eligible for cytoreductive nephrectomy, metastasectomy or post-treatment biopsy.<br>• Measurable disease<br>• ECOG performance status </= 2.<br>• Within 14 days of the first dose of study drug, patients must have adequate organ and marrow function<br>• Men and women >/= 18 years of age<br><br>Exclusion Criteria:<br>• Any other malignancy from which the patient has been disease-free for less than 2 years, except for non-melanoma skin cancer, in situ carcinoma of any site. | Experimental: Arm A - Nivolumab<br>Participants receive Nivolumab 3 mg/kg by vein every 2 weeks for a total of 6 weeks followed by cytoreductive nephrectomy.<br><br>Experimental: Arm B - Nivolumab + Bevacizumab<br>Participants receive Nivolumab at 3 mg/kg by vein every 2 weeks plus Bevacizumab 10 mg/kg by vein every 2 weeks for 6 weeks followed by cytoreductive surgery.<br><br>Experimental: Arm C - Nivolumab + Ipilimumab<br>Participants receive Nivolumab at 3 mg/kg by vein every 3 weeks plus | Primary:<br>Overall Toxicity<br><br>Secondary:<br>Immunological Changes in Tumor Tissues, ORR |

| | | | |
|---|---|---|---|
| | • Patients who have organ allografts.<br>• Patients who have had a major surgical procedure, open biopsy, or significant traumatic injury with poorly healed wound within 6 weeks prior to first dose of study drug;<br>• Known or suspected autoimmune disease.<br>• Patients who have a primary brain tumor, any brain metastases, leptomeningeal disease, seizure disorders not controlled with standard medical therapy, history of stroke within the past year. | Ipilimumab 1 mg/kg by vein every 3 weeks for 6 weeks followed by cytoreductive surgery. | |

Source https://clinicaltrials.gov

# 7 SUPPLEMENTAL QUESTIONS

No Supplemental questions were addressed in this review.

# 8 COMPARISON WITH OTHER LITERATURE

Through the systematic review of the literature, a phase I, open-label, parallel-cohort, dose-escalation study, CheckMate 016,[1] was identified. It is included in this section as supporting evidence for safety.

CheckMate 016[1]

Among the first to investigate the combination of two checkpoint inhibitors for the treatment of a genitourinary malignancy, CheckMate 016 was a phase I, open-label, parallel-cohort, dose-escalation study, aiming to evaluate the safety and efficacy of nivolumab + ipilimumab in combination, and nivolumab + TKI in mRCC. Adult subjects (≥ 18) with histologically confirmed advanced clear-cell RCC or mRCC, measurable disease according to RECIST 1.1 and a KPS of at least 80% at study enrolment were included.

The primary objective was to assess overall safety and tolerability of nivolumab + ipilimumab. Main secondary end points included the best overall response (BOR), ORR, DOR per RECIST 1.1, time to response, PFS and 24-weeks PFS rate.

The study included 5 treatment arms, three of which consisted of the combination of nivolumab plus ipilimumab and are covered here. Subjects received intravenous nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3), or nivolumab 3 mg/kg + ipilimumab 3 mg/kg (N3I3) every three weeks for four doses, followed by nivolumab monotherapy 3 mg/kg every two weeks, until progression or toxicity. Safety and efficacy analyses included all subjects who received one or more doses of study medication.

Results

A total of 194 patients enrolled between February 2012 and May 2014, with 47 each assigned to the N3I1 and N1I3 arms. There were six patients in the N313 arm and one was censored at 6 months, one at 12 months, one at 18 months, and two at 24 months; one patient withdrew consent. Reasons for discontinuation were disease progression (three patients) and treatment related toxicity (two patients).

Baseline demographic and clinical characteristics generally were balanced between the N3I1 and the N1I3 arms. Twenty-five (53.2%) and 21 (44.7%) treatment-naive patients were assigned to the N3I1 and the N1I3 arms, respectively. At data cutoff (March 16, 2016), median follow-up was 22.3 months for both arms, and minimum follow-up was 22 months. Forty-six (97.9%) patients in the N3I1 arm and 42 (89.4%) in the N1I3 arm received ≥90% of the planned nivolumab and ipilimumab dose intensity (ie, four doses) during the induction phase. A total of 63.8% and 70.2% of patients continued onto nivolumab monotherapy in the N3I1 and N1I3 arms, respectively. The median number of nivolumab doses received was 10.0 in the N3I1 arm and 7.0 in the N1I3 arm.

***Safety results (Primary End Point)[1,8]***

In CheckMate 016, the safety data in cohort I-1 (n = 47) demonstrated that nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg had an acceptable safety profile in subjects with RCC.

As of the 16-Mar-2016 DBL, the proportion of treated subjects who had died in the nivolumab 3 mg/kg + ipilimumab 1 mg/kg combination therapy group was 34.0% and disease progression was the most common cause of death (Table 10). No deaths in the nivolumab 3 mg/kg + ipilimumab 1 mg/kg treatment group were attributed to study drug toxicity.

Serious adverse events (SAEs) (regardless of causality) were reported in 61.7% of subjects in cohort I-1 and the most frequently reported all-causality SAE (≥10%) was malignant neoplasm progression (12.8%).[8]Grade 3-4 SAEs were reported in 46.8% of subjects. Drug-related SAEs were reported in 23.4% of subjects and the most frequently reported were diarrhea and pyrexia (6.4% each). Grade 3-4 drug-related SAEs were reported in 19.1% of subjects and the only Grade 3-4 drug-related SAE reported in > 1 subject was diarrhea (reported in 2 subjects, 4.3%).

AEs leading to discontinuation of study treatment were reported in 5 (10.6%) subjects, with 1 event occurring in each subject (amylase increased, blood creatinine increased, lipase increased, autoimmune hepatitis, and sarcoidosis); all were drug-related. Grade 3-4 drug-related AEs leading to discontinuation were reported in 3 (6.4%) subjects, with 1 event occurring in each subject (amylase increased, lipase increased, and autoimmune hepatitis).[8]

Any grade AEs (regardless of causality) were reported in 100% of subjects in cohort I-1 and the most frequently reported were fatigue (66%), cough (53.2%), and arthralgia (51.1%).[8] Grade 3-4 AEs (regardless of causality) were reported in 70.2% of subjects and the most frequently reported was lipase increased (19.1%).[8]

Any grade drug-related AEs were reported in 91.5% of subjects and the most frequently reported were fatigue (51.1%), rash and pruritus (each 31.9%), nausea (27.7%), and arthralgia (25.5%). Grade 3-4 drug-related AEs were reported in 38.3% of subjects and the most frequently reported was lipase increased (14.9%).[1]

The most frequently reported any-grade drug-related select AE categories in the nivolumab 3 mg/kg + ipilimumab 1 mg/kg treatment group were skin (48.9%), endocrine (27.7%), and gastrointestinal (25.5%). The majority of drug-related select AEs were Grade 1-2 and the only Grade 3-4 drug-related select AEs PTs reported in > 1 subject were diarrhea, ALT increased, and AST increased (each reported in 2 subjects).[1]

***Efficacy results (Secondary End Points)***

The median OS was not reached in the N3l1 group and was 32.6 months in the N1l3; the high survival rate in patients receiving the combination of nivolumab + ipilimumab was maintained with a 2-year OS of 67% and 70%, respectively. A substantial level of clinical activity has also been reported, with a confirmed ORR of 40.4% in each group.[1]

**Table 10. Summary of Safety Results, All Nivolumab 3 mg/kg plus Ipilimumab 1 mg/kg Treated Subjects – CheckMate 016[1,8]**

| Number of subjects (%) | IPI1 + NIV3 (Cohort I-1) | |
|---|---|---|
| **Deaths** | 16 (34.0) | |
| Within 30 days of last dose | 0 | |
| Within 100 days of last dose | 3 (6.4) | |
| Due to study drug toxicity | 0 | |
| | **Any Grade** | **Grade 3-4** |
| **All-causality SAEs** | 29 (61.7) | 20 (42.6) |
| **Drug-related SAEs** | 11 (23.4) | 9 (19.1) |
| **All-causality AEs leading to discontinuation** | 5 (10.6) | 3 (6.4) |
| **Drug-related AEs leading to discontinuation** | 5 (10.6) | 3 (6.4) |
| **All-causality AEs** | 47 (100.0) | 33 (70.2) |
| **Drug-related AEs** | 43 (91.5) | 18 (38.3) |
| **Select AEs, by Category** | | |
| **All-causality within 30 Days of Last Dose** | | |
| Endocrine | 14 (29.8) | 3 (6.4) |
| Gastrointestinal | 16 (34.0) | 3 (6.4) |
| Hepatic | 11 ( 23.4) | 3 (6.4) |
| Pulmonary | 3 (6.4) | 0 |
| Renal | 11 (23.4) | 2 (4.3) |
| Skin | 29 (61.7) | 1 (2.1) |
| Hypersensitivity/Infusion Reactions | 5 (10.6) | 0 |
| **Drug-related within 30 Days of Last Dose** | | |
| Endocrine | | |
| Gastrointestinal | 12 (25.5) | 2 (4.3) |
| Hepatic | 9 (19.1) | 3 (6.4) |
| Pulmonary | 3 (6.4) | 0 |
| Renal | 9 (19.1) | 2 (4.3) |
| Skin | 23 (48.9) | 0 |
| Hypersensitivity/Infusion Reactions | 5 (10.6) | 0 |

MedDRA version 18.1; CTC version 4.0. All events are within 100 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AE = adverse event; IPI =, ipilimumab 1 mg/kg; NIV3 = nivolumab 3 mg/kg.

# 9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on nivolumab plus ipilimumab for advanced RCC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

# APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials April 2018, Embase 1974 to 2018 May 16, Ovid MEDLINE(R) ALL 1946 to May 16, 2018

| # | Searches | Results |
|---|---|---|
| 1 | (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN or HSDB8256 or HSDB 8256).ti,ab,ot,kf,kw,hw,rn,nm. | 10425 |
| 2 | (Yervoy* or ipilimumab* or strentarga* or Winglore* or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666).ti,ab,ot,kf,kw,hw,rn,nm. | 14488 |
| 3 | Kidney Neoplasms/ or Carcinoma, Renal Cell/ | 76931 |
| 4 | exp Kidney/ or (kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kf,kw. | 2108192 |
| 5 | exp Neoplasms/ or (cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan* or sarcoma*).ti,ab,kf,kw. | 9014359 |
| 6 | (hypernephroma* or nephroma* or reninoma* or RCC or mRCC).ti,ab,kf,kw. | 43991 |
| 7 | 3 or (4 and 5) or 6 | 401774 |
| 8 | 1 and 2 and 7 | 567 |
| 9 | 8 use medall | 96 |
| 10 | 8 use cctr | 45 |
| 11 | *nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or HSDB8256 or HSDB 8256).ti,ab,kw,dq. | 7239 |
| 12 | *Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or anti-CTLA4 or anti-CTLA-4 or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016).ti,ab,kw,dq. | 9806 |
| 13 | exp Kidney cancer/ | 164093 |

| | | |
|---|---|---|
| 14 | exp Kidney/ or (kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kw,dq. | 2108602 |
| 15 | exp Neoplasm/ or (cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan* or sarcoma*).ti,ab,kw,dq. | 9019345 |
| 16 | (hypernephroma* or nephroma* or reninoma* or RCC or mRCC).ti,ab,kw,dq. | 43943 |
| 17 | 13 or (14 and 15) or 16 | 427012 |
| 18 | 11 and 12 and 17 | 399 |
| 19 | 18 use oemezd | 276 |
| 20 | 19 and conference abstract.pt. | 117 |
| 21 | limit 20 to english language | 117 |
| 22 | limit 21 to yr="2013 -Current" | 115 |
| 23 | 19 not 20 | 159 |
| 24 | 9 or 10 or 23 | 300 |
| 25 | limit 24 to english language | 267 |
| 26 | remove duplicates from 25 | 191 |
| 27 | 26 or 22 | 306 |

**2. Literature search via PubMed**

A limited PubMed search was performed to capture records not found in MEDLINE.

| Search | Query | Items found |
|---|---|---|
| #8 | Search #7 AND publisher[sb] Filters: English | 3 |
| #7 | Search #1 AND #2 AND #6 Filters: English | 77 |
| #6 | Search #3 OR #4 OR #5 Filters: English | 125668 |
| #5 | Search Hypernephroma*[tiab] OR nephroma*[tiab] OR reninoma*[tiab] OR RCC[tiab] OR mRCC[tiab] Filters: English | 14550 |

| Search | Query | Items found |
|---|---|---|
| #4 | Search (Kidney[mh] or kidney*[tiab] OR renal[tiab] OR hypernephroid[tiab] OR collecting duct*[tiab] OR Grawitz[tiab] OR nephroid[tiab]) AND (exp Neoplasms[mh] or cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR pyelocarcinoma*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR metast*[tiab] OR malignan*[tiab] OR sarcoma*[tiab]) Filters: English | 112523 |
| #3 | Search Kidney Neoplasms[mh:noexp] OR Carcinoma, Renal Cell[mh] Filters: English | 50648 |
| #2 | Search Ipilimumab[supplementary concept] OR ipilimumab*[tiab] OR Yervoy*[tiab] OR Winglore*[tiab] OR anti-CTLA4[tiab] OR anti-CTLA-4[tiab] or MDX-CTLA 4[tiab] OR MDX-CTLA4[tiab] OR MDXCTLA-4[tiab] OR MDXCTLA4[tiab] OR MDX-010[tiab] OR MDX010[tiab] OR MDX101[tiab] OR MDX 101[tiab] OR BMS734016[tiab] OR BMS 734016[tiab] Filters: English | 2928 |
| #1 | Search Nivolumab[supplementary concept] OR Opdivo*[tiab] OR nivolumab[nm] OR nivolumab[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab] OR 31YO63LBSN[rn] OR HSDB8256[tiab] OR HSDB 8256[tiab] Filters: English | 2045 |

3. Cochrane Central Register of Controlled Trials (Central)

   Searched via Ovid

4. Grey Literature search via:

**Clinical Trial Registries:**

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Opdivo (nivolumab)/Yervoy (ipilimumab)/RCC

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Opdivo (nivolumab)/Yervoy (ipilimumab)/RCC

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org

Search: Opdivo (nivolumab)/Yervoy (ipilimumab)/RCC – last 5 years

**Detailed Methododolgy**

The literature search was performed by the pCODR Methods Team using the search strategy provided above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2018 May 16) with in-process records & daily updates via Ovid; Embase (1974-2018 May 16) via Ovid; The Cochrane Central Register of Controlled Trials (April 2018) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Opdivo (nivolumab), Yervoy (ipilimumab) and renal cell carcinoma.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of August 2, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

## Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

## Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

## Data Analysis

No additional data analyses were conducted as part of the pCODR review.

## Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

# REFERENCES


1. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 study. *J Clin Oncol*. 2017;35(34):3851-3858.

2. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *New Eng J Med*. 2018;378(14):1277-1290.

3. Cella D, Grunwald V, Escudier B, et al. Quality of life in patients with advanced renal cell carcinoma in the randomized, open-label CheckMate 214 trial [slide deck]. In: pan-Canadian Oncology Drug Review manufacturer submission: Opdivo (nivolumab) and Yervoy (ipilimumab), 10 mg nivolumab/mL in 40 mg and 100 mg single-use vials for intravenous infusion. St-Laurent (QC): Bristol-Myers Squibb Canada; 2018.

4. Cella D, Grunwald V, Escudier B, et al. Quality of life in patients with advanced renal cell carcinoma in the randomized, open-label CheckMate 214 trial [abstract]. *J Clin Oncol*. 2018;36(15 Suppl):abstr 3037.

5. Tannir NM, Hammers HJ, Amin A, et al. Characterization of the benefit-risk profile of nivolumab + ipilimumab (N+I) v sunitinib (S) for treatment-naïve advanced renal cell carcinoma (aRCC; CheckMate 214) [poster]. In: pan-Canadian Oncology Drug Review manufacturer submission: Opdivo (nivolumab) and Yervoy (ipilimumab), 10 mg nivolumab/mL in 40 mg and 100 mg single-use vials for intravenous infusion. St. Laurent (QC): Bristol-Myers Squibb Canada; 2018.

6. Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: Efficacy and safety of nivolumab 1 ipilimumab (N1I) v sunitinib (S) for treatment-naive advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups. *Ann Oncol*. 2017;28 (Supplement 5):v621-v622.

7. Vyas C, Motzer RJ, Tannir NM, et al. Nivolumab + ipilimumab (n+i) vs sunitinib (s) for treatment-naive advanced or metastatic renal cell carcinoma (arcc): Results from checkmate 214, including overall survival by subgroups [abstract]. *J Oncol Pharm Pract*. 2018;24(5 Suppl 1):17-18. Presented at: Canadian Association of Pharmacy in Oncology Conference; May 12-16, 2018; Gatineau, QC.

8. pan-Canadian Oncology Drug Review manufacturer submission: Opdivo (nivolumab) and Yervoy (ipilimumab), 10 mg nivolumab/mL in 40 mg and 100 mg single-use vials for intravenous infusion. St-Laurent (QC): Bristol-Myers Squibb Canada; 2018.

9. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. http://www.cancer.ca/Canadian-Cancer-Statistics-2017-EN.pdf. Accessed Jun 6, 2018.

10. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer*. 2008;113(1):78-83.

11. Jewett MA, Knox JJ, Kollmansberger C, Basiuk J. Canadian kidney cancer forum 2008. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2494888 Accessed Jun 6, 2018

12. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115-124.

13. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369(8):722-731.

14. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356(22):2271-2281.

15. Gleave M, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *N Engl J Med* 1998;338(18):1265-1271.

16. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. *N Engl J Med*. 1998;338(18):1272-1278.

17. Negrier S, Perol D, Ravaud A, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer*. 2007;110(11):2468-2477.

18. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27(34):5794-5799.

19. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23(4):832-841.

20. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002;20(1):289-296.

21. Rini BI. VEGF-targeted therapy in metastatic renal cell carcinoma. *Oncologist*. 2005;10(3):191-197.

22. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy *N Engl J Med* 2016;375(23):2246-2254.

23. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.

24. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer*. 2010;116(18):4256-4265.

25. Motzer RJ, Escudier B, Oudard S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet*. 2013;14(6):552-562.

26. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.

27. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.

28. Motzer RJ, Sharma P, McDermott DF, et al. CheckMate 025 phase III trial: outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC) [abstract]. *J Clin Oncol*. 2016;34(Suppl 25):Abstr 498. Presented at: Genitourinary Cancers Symposium; Jan 2016; San Francisco, CA.

29. Albiges L, Fay AP, Xie W, et al. Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma. *Eur J Cancer*. 2015;51(17):2580-2586.

30. pan-Canadian Oncology Drug Review checkpoint meeting: Opdivo (nivolumab) and Yervoy (ipilimumab). Bristol-Myers Squibb response to pCODR request for additional information. St. Laurent (QC): Bristol-Myers Squibb; 2018.

31. [Pr]Opdivo® (nivolumab) for intravenous infusion, 10 mg nivolumab/mL, 40 mg and 100 mg single-use vials [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2018.