pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Metastatic Renal Cell Carcinoma

September 1, 2016

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TABLE OF CONTENTS

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of nivolumab monotherapy on patient outcomes in the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior systemic therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one phase III, open-label, multicenter trial (CheckMate 025) which randomised patients to receive nivolumab 3 mg per kilogram of body weight per 2 weeks (mg/kg) (n=410), administered intravenously, or everolimus 10 mg taken orally daily (n=411). The study treatments were continued until disease progression, unacceptable toxic effects arose, the patient withdrew consent or the study ended.

The baseline demographic and clinical characteristics of the patients were well-balanced between the two study groups. The trial recruited adult patients (≥18 years of age) with histologically proven advanced or metastatic RCC and Karnofsky performance status ≥ 70, who had previously been treated with one or two antiangiogenic treatment regimens, and showed evidence of disease progression within 6 months of enrollment.

Efficacy

The primary endpoint of the study was overall survival (OS). The trial stopped early, in July 2015, after meeting its primary endpoint, and the patients in the everolimus group were allowed to cross-over to receive nivolumab. The median OS was statistically higher in the nivolumab group than that in the everolimus group (25.0 versus 19.6 months; HR= 0.73, 95% CI 0.57 to 0.93; p=0.002). The OS benefit was consistent across most patient subgroups.[1] The observed OS benefit was also not affected by PD-L1 expression status.[1]

Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), adverse events (AEs) and patient-reported outcomes. The median PFS reached 4.6 in the nivolumab group and 4.4 in the everolimus group (HR= 0.88, 95% CI 0.75 to 1.03; p=0.11). ORR was also found to be statistically higher with nivolumab than with everolimus (25% versus 5%; odds ratio= 5.98; 95% CI 3.68 to 9.72; p<0.001).

Harms

AEs of any grade were comparable between the two arms (79% and 88% in the nivolumab- and everolimus-treated patients, respectively); while the rate of grade 3 or 4 AEs was lower in the nivolumab group when compared to that of the everolimus group (19% vs. 37%, respectively).[1]

1.2.2 Additional Evidence

pCODR received input on nivolumab (Opdivo) for patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior systemic therapy from one patient advocacy group, Kidney Cancer Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

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No supplemental question was identified during development of the review.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2015, there were 6200 new cases and 1,800 deaths due to the disease (Canadian Cancer Society Statistics 2015). About 90% of kidney cancers are renal cell cancers (RCC). About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers. At presentation 75% of patients with RCC will have localized disease, while about 25% are already metastatic. Of the patients diagnosed with localized disease, 30-50% 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.[2]

After failure of tyrosine kinase inhibitor first-line therapy, everolimus and axitinib are the available standard second-line options.[3,4] Both drugs were approved based on a modest progression-free survival benefit rather than an overall survival benefit. The use of both tyrosine kinase inhibitors and mTOR inhibitors is also limited by their toxicity which includes fatigue, hand-foot syndrome, hypertension, hypothyroidism, diarrhea, and mucositis, skin rash and pneumonits as the clinically most relevant. 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. Thus, there still is an unmet need for novel therapies in the treatment of metastatic RCC, which are associated with increased efficacy and in particular increased overall survival.

Effectiveness

Based on the results of the CheckMate 025 trial nivolumab demonstrated a statistically significant and, more importantly, clinically meaningful overall survival benefit. The overall survival benefit with nivolumab was observed across most pre-specified subgroups, including region, MSKCC prognostic score, PD-L1 expression, presence of liver/bone metastases and number of previous regimens of antiangiogenic therapy. This is the only randomized study in the second-line setting with an overall survival endpoint (and only the second one overall in the era of targeted therapies). Additionally this is the first randomized study in the second-line setting of metastatic kidney cancer ever with a clear overall survival benefit and these results clearly place nivolumab among the most active therapies for metastatic RCC.

The objective response rate was higher with nivolumab than with everolimus, the highest objective response rate ever reported in the second-line setting. Progression-free survival was similar in both groups.

Nivolumab was very well tolerated with a significant benefit in quality of life over everolimus. This is particularly important for patients with metastatic RCC, many of whom have already a number of tumor progression related symptoms at the time of nivolumab treatment initiation. In particular, the number of immune-related adverse events such as colitis, hepatitis or hypophysitis were extremely rare.

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1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to nivolumab in the second-line / third-line treatment of advanced and metastatic RCC based on one high-quality randomized controlled trial that demonstrated a clinically meaningful and statistically significant benefit in overall survival for nivolumab compared with everolimus. This was based on CheckMate 025 which supports the use of nivolumab after one or two prior TKIs in patients with clear cell or clear cell component carcinoma. Nivolumab should therefore replace everolimus in the second-line setting after prior anti-angiogenic therapy. Based on previous experience with TKis, the excellent tolerability of nivolumab and the high unmet need for these patients, performance status > 1 or the presence of brain metastases should not exclude patients from nivolumab treatment.

In making this recommendation, the Clinical Guidance Panel considered:

- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC presents with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC who have failed first-line therapy. Everolimus and axitinib are the only drugs available. Both agents were approved based on a PFS benefit and both drugs are associated with a number of substantial side effects, including hypertension, fatigue, diarrhea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes. Hence there is an urgent need for better treatment options in RCC.
- Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that PD-1 inhibitors and immunotherapy will have activity in non-clear cell RCC. Nivolumab should therefore be made available to patients with non-clear-cell histology.
- In contrast to TKIs or mTOR inhibitors, nivolumab is very well tolerated, which will safely allow treatment for patients with performance status > 1. This is consistent with current clinical practice where patients with performance status 2 or 3 are treated with tyrosine kinase inhibitors such as sunitinib and have shown a good benefit even in although these patients were initially excluded from the pivotal studies.
- Given the completely different mechanism of action of nivolumab compared to targeted agents there is no reason why patients with more than 2 prior lines of targeted therapies should not respond to nivolumab. It is however expected that nivolumab will rapidly become the standard in second-line and will therefore make the question of activity after several lines of targeted therapies quickly irrelevant.
- In clinical practice, patients with brain metastases are treated the same way as patients without brain metastases. Therefore patients with brain metastases should not be excluded from treatment with nivolumab.
- The results of this trial are not generalizable to the first-line situation and should await randomized trials in the first-line setting which are currently ongoing.
- It is of utmost importance to recognize pseudoprogression in order to not stop an active therapy in RCC patients. Checkmate-025 accounted for this phenomena by permitting treatment beyond progression. True progression was defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

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2 CLINICAL GUIDANCE

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) in advanced or metastatic renal cell carcinoma. 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 pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding nivolumab (Opdivo) conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on nivolumab and a summary of submitted Provincial Advisory Group Input on nivolumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Kidney cancer represents about 3% of all cancers in Canada. In 2015, the estimates of new cases of kidney cancer and deaths from this disease in Canada, were 6200 and 1800, respectively.[5] Approximately 90% of kidney cancer originate from tubular cells of kidney and are identified as renal cell carcinoma (RCC). RCC is classified histologically as clear-cell histology (80%) or non-clear cell cancers (20%) which include papillary, sarcomatoid, and chromophobe subtypes amongst others. Up to 25% of all patients with RCC present with distant metastases at the time of initial diagnosis. Patients with extensive disease have a poorer prognosis, when compared to localized disease (50-60% survival rate in advanced disease versus 70-90% I localized tumors).[2]

In patients with advanced metastatic RCC, who have already experienced treatment failure after previous chemotherapy, everolimus (an oral mammalian target of rapamycin (mTOR) inhibitor) and axitinib (an oral vascular endothelial growth factor (VEGF) receptors inhibitor) are considered standard treatment option based on a significant progression-free survival benefit.[4,6] However, the use of these drugs have been limited by their toxicity .[4,6]

Nivolumab -a fully human immunoglobulin (Ig) G4 programmed death1 (PD–1) immune checkpoint inhibitor- is a new treatment option that is currently under review. This antibody restores the T-cell antitumor activity by blocking the interaction between PD-1 and PD-1 ligand 1 (PD-L1) and PD-L2 (a mechanism that normally leads to inhibition of cellular immune response).[7]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the safety and efficacy of nivolumab (Opdivo) monotherapy for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior systemic therapy.

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2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

The efficacy and safety of nivolumab 3 mg per kilogram of body weight (mg/kg) (n=410), administered intravenously, was compared to everolimus 10 mg taken orally daily (n=411) in an international, phase III, open-label, multicenter trial (CheckMate 025).[1,8-10] The study recruited adult patients (≥18 years of age) with histologically proven advanced or metastatic RCC and Karnofsky performance status ≥ 70, who had previously been treated with one or two antiangiogenic treatment regimens, and showed evidence of disease progression within 6 months before enrollment on the CheckMate 025 study. The baseline demographic and clinical characteristics of the patients were well-balanced between the two study groups. The study treatments were continued until disease progression, unacceptable toxic effects arose, the patient withdrew consent or the study ended. The primary endpoint of the study was overall survival (OS), and the secondary endpoints included objective response rate (ORR), progression-free survival (PFS), adverse events (AEs) and patient-reported outcomes. As shown in Table 2.1, efficacy analyses were based on the intent-to-treat population, which consisted of all patients who were randomly assigned to the study treatments (410 and 411, in the nivolumab and everolimus arms, respectively), while the safety analyses were conducted in randomized patients who had received at least one dose of the study treatment (406 and 397, in the nivolumab and everolimus arms, respectively).

The trial stopped early, in July 2015, after meeting its primary endpoint, and the patients in the everolimus group were allowed to cross-over to receive nivolumab. At the interim analysis data cut-off date (June 2015), 17% of the patients treated in the nivolumab group (67 of 406) 7% of those treated in the everolimus group (28 of 397) continued to receive treatment.[11]

Table 2.1 - CheckMate 025 Study Population

	Nivolumab (Opdivo)	Everolimus (Affinitor)
Randomized (efficacy analysis population)	**410 (100%)**	**411 (100%)**
Treated (safety analysis population)	406 (99%)	397 (97%)
Alive at planned interim analysis	227 (55%)	196 (48%)

Efficacy outcomes

A summary of the key efficacy analyses is shown in Table 2.2. After a minimum follow up period of 14 months, the median OS was statistically higher in the nivolumab group than that in the everolimus group (25.0 versus 19.6 months; HR= 0.73, 95% CI 0.57 to 0.93; p=0.002). The OS benefit was consistent across most patient subgroups, defined based on geography, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk score and number of prior chemotherapy regimens.[1] Additional subgroup analyses of OS, after a median follow up of 17-18 months, showed consistent OS benefit associated with nivolumab across the subgroups of number and sites of metastasis, previous treatments, and Karnofsky performance status.[9] The observed OS benefit was also not affected by PD-L1 expression status.[1]

The median PFS reached 4.6 in the nivolumab group and 4.4 in the everolimus group (HR= 0.88, 95% CI 0.75 to 1.03; p=0.11). The investigators observed a delayed separation of the PFS Kaplan-Meier curves, and hence, performed a sensitivity analysis of patients whose disease had not progressed at 6 months, to further examine the PFS results. This ad-hoc sensitivity analysis showed a statistically higher median PFS with nivolumab than with everolimus (15.6 versus 11.7 months; HR= 0.64; 95% CI 0.47 to 0.88).[1] The results of an ad-hoc sensitivity analysis of PFS that was limited to study participants for whom disease progression or death outcomes had not

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occurred at the 6 months (35% and 31% patients in the nivolumab and everolimus arms, respectively), showed a median PFS of 15.6 months (95% CI 11.8 to 19.6) with nivolumab and 11.7 months (95% CI 10.9 to 14.7) with everolimus (HR= 0.64; 95% CI 0.47 to 0.88).[1]

ORR was found to be statistically higher with nivolumab than with everolimus (25% versus 5%; odds ratio= 5.98; 95% CI 3.68 to 9.72; p<0.001). The numbers of patients with a partial response were 99 (24%) in the nivolumab group and 20 (5%) in the everolimus group. Four patients in the nivolumab group (1%) and 2 in the everolimus group (<1%) had a compete response. The median time to response was 3.5 months with nivolumab and 3.7 months with everolimus. The median duration of the response was 12.0 months in both study groups.[1]

Patient-reported outcomes (PRO's)

As shown in Table 2.2, an improvement in patient-reported outcomes was reported in the nivolumab group, in a consistent manner, at each assessment after baseline for patients in the nivolumab group, when compared with the everolimus group (p<0.05).[1]

Harm outcomes

AEs of any grade were comparable between the two arms (79% and 88% in the nivolumab- and everolimus-treated patients, respectively); while the rate of grade 3 or 4 AEs was lower in the nivolumab group (19%), when compared to that of the everolimus group (37%).[1] More details about the commonly reported AEs can be found in section 6.3.2.2.

Table 2.2- Summary of the Key Study Results from CheckMate 025 trial

Efficacy outcomes	Nivolumab (n=410)	Everolimus (n=411)
Primary Endpoint		
OS		
Median OS (95% CI), months	25 (21.8-NE)	19.6 (17.6-23.1)
Events (%)	183(44.6)	215 (52.3)
HR (98.5% CI)	0.73 (0.57-0.93)	
P-value (log-rank)	P=0.002	
Secondary Endpoints		
PFS		
Median PFS (95% CI), months	4.6 (3.7-5.4)	4.4 (3.7-5.5)
Events (%)	318 (77.6)	322 (78.3)
HR (95% CI)	0.88 (0.75-1.03)	
P-value (log-rank)	0.11	
ORR		
ORR (%)	25	5
OR(95% CI)	5.98 (3.68-9.72)	
P-value (Cochran-Mantel-Haenszel)	P<0.001	
Median time to response, months	3.5	3.7
Median duration of response, months	12	12
Patient Reported Outcomes		
Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-DRS)		
Baseline score		
Number available for questionnaire	361	343
Completion rate (%)	89%	86%
Median baseline score	31	31
12 months		
Number available for questionnaire	98	63
Completion rate (%)†	80%	81%
Median change from baseline	1 (-9 to 17)	0 (-10 to 20)

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Table 2.2- Summary of the Key Study Results from CheckMate 025 trial		
Efficacy outcomes	Nivolumab (n=410)	Everolimus (n=411)
24 months		
Number available for questionnaire	20	9
Completion rate (%)†	77%	90%
Median change from baseline	2 (-1 to 16)	-2 (-7 to 15)
Harm outcomes	Nivolumab (n=406)	Everolimus (n=397)
Median duration of treatment (95% CI), months	5.5 (<0.1-29.6)	3.7 (0.2-25.7)
Dose Delay (%)	207 (51)	262 (66)
≥1 dose reduction (%)	Not allowed	102 (26)
Discontinuation due to toxicity (%)	31 (8)	52 (13)
All grade AEs (%)	319 (79)	349 (88)
Grade 3/4 AEs	76 (19)	145 (37)

AE= adverse event; **CI**= confidence interval; **HR**= hazard ratio; **NE**= not estimable; **ORR**= objective response rate; **OS**= overall survival; **PFS**= progression free survival
†completion rate= # patients with non-missing data at baseline and at least one follow-up visit divided by # patients in the study at each respective time point.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

Two pivotal early phase trials were identified investigating the effects of nivolumab monotherapy in previously treated advanced-stage cancer patients. Patients within these studies included those that had previously received three or four prior systemic therapies:

A phase I trial by Topalian et al.[12] assessed the safety, antitumor activity and pharmacokinetics of nivolumab in patients with advanced melanoma, non-small-cell lung cancer, castration-resistant prostate cancer, colorectal cancer, or RCC. In this study, 296 adult patients with solid tumors were enrolled to receive nivolumab at a dose of 0.1 to 10.0 mg/kg every 2 weeks of each 8-week treatment cycles (up to 12 cycles) until disease progression or a complete response occurred. Patients were eligible for this trial if they had documented advanced solid tumors with a life expectancy of 12 weeks or longer; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (asymptomatic disease), 1 (restricted in strenuous activity), or 2 (ambulatory but unable to work); measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST); adequate hematologic, hepatic, and renal function; and a history of one to five systemic treatment regimens. Patients with a history of chronic autoimmune disease, chronic infections, or prior immunosuppressive therapies, were excluded.

Among 34 patients with metastatic RCC, 29% had received one, 26% two, 15% three, and 29% four prior systemic antiangiogenic treatments. Nivolumab demonstrated a progression-free survival rate of 56% (95% CI 39% to 73%) the cumulative response rate was 27% (9 of 33 patients; 95% CI 13% to 46%). The objective response rate was 24% (4 of 17 patients) in RCC patients who were treated with a dose of 1.0 mg/kg and 31% (5 of 16 patients) in those treated with 10.0 mg/kg of nivolumab. Of 8 patients with objective responses who had a follow up period of one year or greater, 5 had a durable response, as measured by RECIST criteria; and additional 9 patients (27%) had a stable disease that lasted 24 weeks or longer. The most common drug-related adverse events, regardless of cancer type, were fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Grade 3 or 4 drug-related AEs were reported in 14% (41 of 296) of patients. Three

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treatment-related deaths occurred due to pulmonary toxicity. Severity of the AEs was reported to be similar across various dose levels.

A randomized, dose-ranging phase II trial by Motzer el al.[13] assessed the anti-tumor activity, dose-response relationship and safety of nivolumab in previously treated metastatic RCC patients. The eligibility criteria included histologic confirmation of clear-cell RCC, measurable disease defined by RECIST, prior treatment with at least one antiangiogenic therapy, disease progression during or after last therapy received and within 6 months of enrollment, and Karnofsky performance status ≥ 70%. The study excluded patients active CNS metastases, autoimmune disease, previous therapy with a T-cell co-stimulation or checkpoint inhibitor, or treatment with more than three prior treatment regimens in the metastatic setting. In this study, 168 eligible patients were randomly assigned in a 1:1:1 ratio to receive 0.3, 2, or 10 mg/kg intravenous nivolumab every 3 weeks.

The baseline characteristics of the study arms were well balanced. Overall, 30% of the patients had received one, 37% two, and 33% three or more prior systemic treatments. Progression-free survival (primary study outcome) was reported to be 2.7 months (80% CI, 1.9 to 3.0 months), 4.0 months (80% CI, 2.8 to 4.2 months), and 4.2 months (80% CI, 2.8 to 5.5 months) in the 0.3-, 2-, and 10 mg/kg arms, respectively, with no dose-response relationship (test for trend test P = 0.9). Objective response rates were 20%, 22%, and 20% in the 0.3, 2, and 10 mg/kg arms, respectively (test for trend P = 1.0). More than 50% of responders with all doses had objective responses that lasted more than 12 months. Median overall survival reached 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months) in the 0.3, 2, and 10-mg/kg arms, respectively. The incidence of drug-related AEs of any grade was similar across different doses (75%, 67%, and 78% in the 0.3, 2, and 10 mg/kg arms, respectively), with fatigue being the most commonly experienced AE in each arm. Grade 3 or 4 drug-related AEs occurred in 19/167 patients (11%), and the treatment was discontinued due to AEs in 7% of the nivolumab-treated patients.

Unlike the CheckMate025 phase III trial which aimed to evaluate the performance of nivolumab in comparison to a viable second-line standard treatment (everolimus) for RCC, the above-mentioned studies aimed at evaluating the activity and toxicity of nivolumab in a single cohort of eligible patients receiving nivolumab monotherapy,[12] or comparing the efficacy and safety of three dose levels of nivolumab monotherapy.[13] In addition, it should be noted that the phase I trial[12] included patients with various types of cancer, and that the number of enrolled patients with advanced RCC might not be adequate for evaluating the specific effects of nivolumab in this type of cancer.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

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2.1.6 Other Considerations

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

Patient Advocacy Group Input

From a patient's perspective, pain and mobility were ranked the highest in terms of aspects of kidney cancer important to control, followed by fatigue and shortness of breath. Respondents indicated that these symptoms impact on their day-to-day activities, including their ability to work, travel, exercise, conduct household chores, fulfill family obligations and ability to spend time with family and friends. Drug therapies used to treat kidney cancer (other than nivolumab) included sunitinib, pazopanib, everolimus, axitinib, high dose interleukin 2, sorafenib, temsirolimus, bevacizumab in combination with erlotinib, bevacizumab in combination with CRLX101, savolitinib, carboplatin & gemcitabine, and clinical trial drug. The most common side effects experienced from these treatments were fatigue, followed by diarrhea and loss of appetite.

According to Kidney Cancer Canada, respondents who have not used nivolumab expect that this therapy would provide for long-term stability or reduction of disease; improvement to physical condition such as decreasing the size of or stabilizing the tumour, reducing pain, improving breathing. Respondents also stated that improvement to quality of life were extremely important if they were to consider taking a new therapy for their kidney cancer. Respondents who have experience with nivolumab rated their quality of life as high while on treatment. Overall, 76% of respondents rated side effects of nivolumab as tolerable; these side effects include, fatigue, decreased appetite, and pain in muscles, bones and joints. Kidney Cancer Canada noted that in many cases, a large proportion (>60%) of respondents selected "N/A", suggesting that the following side effects (e.g., diarrhea, nausea, injection-related side-effects at the time of infusion, flu-like symptoms, and hand-foot syndrome) may not apply to them. While these side effects appear to be more tolerable, Kidney Cancer Canada acknowledges that when they do occur it progresses quickly with possible long term negative health outcomes.

Kidney Cancer Canada highlighted that patients require choice in second-line therapy to continue managing their disease and side effects and to maintain quality of life.

PAG Input

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

Clinical factors:

- Indication creep into first line setting
- Unknown treatment duration

Economic factors:

- Drug wastage
- Frequency of administration and clinic visits
- Intravenous treatment where oral treatments are currently available

Please see Section 5 for more details.

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Table 2.3. Assessment of generalizability of evidence for nivolumab in advanced or metastatic renal cell carcinoma				
Domain	**Factor**	**Evidence (CheckMate 025 trial)**	**Generalizability Question**	**CGP Assessment of Generalizability**
Population	Histologic type of disease	The CheckMate 025 trial limited its inclusion criteria to patients with confirmed clear cell RCC.	Are the trial results generalizable to other types of RCC (i.e., non-clear cell carcinoma)?	Non-clear cell RCC is rare and patients with non-clear cell renal cell carcinoma represent a particularly difficult group. 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. While the results of CheckMate-025 are not generalizable to non-clear cell RCC it is expected that PD-1 inhibitors and immunotherapy will have activity in non-clear cell RCC as well and nivolumab should be made available to patients with clear-cell histology.
	Karnofsky Performance Status (KPS)	In the CheckMate 025 trial patients with a KPS< 70 were excluded.	Do the trial results apply to patients with a KPS less than 70? If so, why?	Real world data with tyrosine kinase inhibitors such as sunitinib have shown a good benefit for TKIs even in patients with performance status 2 or 3 although these patients were initially excluded from the pivotal studies. There is no biologic reason why patients with performance status > 1 should respond differently to nivolumab. In contrast to TKIs or mTOR inhibitors, nivolumab is very well tolerated, which will safely allow treatment for patients with performance status > 1. In a subset analysis of this trial, nivolumab actually was associated with higher OS benefit in patients with poor-risk disease (HR=0.47; 95% CI 0.30 to 0.73). This is consistent with data from other studies showing good results in patients with sarcomatoid differentiation that is generally associated with more aggressive RCC.
	Number of previous chemotherapy regimes	In the checkmate 025 trial, patients who had been treated with more than two chemotherapy regimens were excluded. PAG identified that nivolumab may also be used in patients who have received three	Do the trial results apply to patients who have been treated with more than two chemotherapy regimens? If so, why?	Given the completely different mechanism of action of nivolumab compared to targeted agents there is no reason why patients with more than 2 prior lines of targeted therapies should not respond to nivolumab. In fact, significant activity was seen in earlier studies which included patients with multiple lines of prior therapy.[12,13] Given the activity of nivolumab it is expected that nivolumab will rapidly become the standard in second-line and will therefore make the question of activity after several lines of targeted therapies quickly irrelevant.

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Table 2.3. Assessment of generalizability of evidence for nivolumab in advanced or metastatic renal cell carcinoma				
Domain	**Factor**	**Evidence (CheckMate 025 trial)**	**Generalizability Question**	**CGP Assessment of Generalizability**
		previous treatments (as fourth-line therapy).		
	Metastatic Sites	In the CheckMate 025 trial, patients with CNS metastases were excluded.	Does the exclusion of patients with CNS metastatic disease limit the generalizability of the trial results to Canadian patients?	Patients with brain metastases are typically excluded from clinical trials because they carry a worse prognosis and have a higher risk of bleeding in these metastases if not properly treated e.g. with radiation. Real world data with TKIs and mTOR inhibitors have demonstrated a benefit even for these patients.[14] Today in clinical practice, patients with brain metastases are treated the same way as patients without brain metastases. Therefore patients with brain metastases should not be excluded from treatment with nivolumab.
Intervention	Line of therapy	In the CheckMate 025 trial studied nivolumab in second-line and third-line therapy for patients with advanced or metastatic RCC. PAG has identified an interest among clinicians and patients to use nivolumab in the first line setting.	Are the results of the trial generalizable to first line therapy?	The results of this trial are not generalizable to the first-line situation. Randomized trials in the first-line setting are currently ongoing and will determine the value of immunotherapy in the first-line setting.
CNS= central nervous system; PAG= Provincial Advisory Group; RCC= renal cell carcinoma				

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2.2 Interpretation and Guidance

Burden of Illness and Need

The management of metastatic renal cell carcinoma has undergone tremendous change in the past 5-8 years. An increasing understanding of the disease biology has translated into the development of various new therapeutic approaches. Targeted agents such as the small molecule tyrosine kinase inhibitors: sunitinib, sorafenib, pazopanib and axitinib; the mTOR inhibitors: everolimus and temsirolimus; and the monoclonal antibody bevacizumab have shown significant activity in the treatment of this disease.[15]

Sunitinib and Pazopanib are the most commonly used first-line treatment options.[16,17] Everolimus and axitinib are the available standard second-line options.[3,4] Both drugs were approved based on a progression-free survival benefit rather than an overall survival benefit. The benefit in progression-free survival is modest. For everolimus PFS was 4.9 versus 1.9 months for placebo in a large randomized phase III trial while for axitinib progression-free survival was 4.8 versus 3.4 months for sorafenib in patients who had failed prior sunitinib therapy. Thus, there still is an unmet need for novel therapies in the treatment of metastatic RCC, which are associated with increased efficacy and in particular increased overall survival.

Effectiveness:

In CheckMate 025 nivolumab was randomized against everolimus in a large open-label phase III study including 821 patients.[1] This was a well conducted randomized trial. Everolimus as one of the two standard second-line treatment options represents an appropriate comparator for this clinical scenario. Main inclusion criteria were comparable to the inclusion criteria of other randomized trials in this setting, namely the everolimus versus placebo (RECORD-1) and axitinib versus sorafenib trial (AXIS) and included clear cell or clear cell component, good performance status, absence of brain metastases and 1 or 2 prior lines of TKI therapy among others. Patient characteristics were well balanced between the 2 groups and are consistent with the characteristics of a real life patient population. Seventy-two percent of patients had previously failed one and 28% had failed two TKIs. In addition, the majority of patients had been recruited in North America (including Canada) or Western Europe which makes the results fully applicable to a Canadian patient population.

It is important to note that the primary endpoint of this study was overall survival. This is the only randomized study in the second-line setting with an overall survival endpoint and only the second one overall in the era of targeted therapies.

The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) in the nivolumab group and 19.6 months (95% CI, 17.6 to 23.1) in the everolimus group. The hazard ratio for death (from any cause) with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the pre-specified criterion for superiority. This represents a statistically significant and, more importantly, clinically meaningful overall survival benefit in favor of nivolumab. The overall survival benefit with nivolumab was observed across most pre-specified subgroups, including region, MSKCC prognostic score, PD-1 expression, presence of liver/bone metastases and number of previous regimens of antiangiogenic therapy. This is the first randomized study in the second-line setting of metastatic kidney cancer ever with a clear overall survival benefit and these results clearly place nivolumab among the most active therapies for metastatic RCC.

The objective response rate was higher with nivolumab than with everolimus (25% vs. 5%; odds ratio 5.98; 95% CI, 3.68 to 9.72; P<0.001). This is the highest objective response rate ever

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reported in the second-line setting. In addition, 34% of patients had stable disease on Nivolumab resulting in a tumor control rate (CR+PR+SD) of 59%.

Interestingly, progression-free survival was similar in both groups, with a median progression-free survival of 4.6 months in the nivolumab group and 4.4 months in the everolimus group. However, the authors performed an adhoc sensitivity analysis including patients who had not progressed or died at 6 months. A clear separation of these curves was seen in favor of nivolumab. These patients probably contributed to the overall survival benefit that was observed with nivolumab in this study. A similar phenomenon has previously been observed with immunotherapy for melanoma where overall survival benefit appears to be driven by a group of long-term survivors. Approximately 20-25% of patients across all ipilumumab studies in melanoma appear to be long-term survivors.[18] Given the similarities between RCC and melanoma with respect to immunotherapy and clinical behavior, a similar effect can be expected in RCC. True progression was defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

Two response patterns relatively new and associated with immunotherapy include responses after an initial increase in total tumor burden ("pseudoprogression") and a reduction in total tumor burden during or after the appearance of new lesion(s) at time points later than week 12 ("pseudoprogression"). It is of utmost importance to recognize pseudoprogression in order to not stop an active therapy in RCC patients. Checkmate-025 accounted for this phenomena by permitting treatment beyond progression. Similar to the observation of pseudoprogression in other cancers (ie. Melanoma) data from an earlier study (Checkmate010) indicate that this is a not negligible phenomenon in RCC.[38] The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with the immunotherapy agent.

Nivolumab was very well tolerated with a significant benefit in quality of life over everolimus. This is particularly important for patients with metastatic RCC, many of whom have already a number of tumor progression related symptoms at the time of nivolumab treatment initiation. In particular, the number of immune-related adverse events such as colitis, hepatitis or hypophysitis were extremely rare.

No reliable predictive biomarker is yet available which would allow the proper selection of patients for anti-PD-1 therapy as there appears to exist prominent interassay variability or discordance among different antibodies used for measurement of PD-L1 expression.[19] In CheckMate 025 PD-L1 expression was not associated with response or survival in the current study and hence PD-L1 expression level cannot be used to select patients. Patients appeared to benefit independent of PD-L1 expression. A similar lack of predictive value for PD-L1 expression has been observed in other tumor types.

Several issues have been raised regarding the generalization and applicability of these results to certain patient populations:

The current study was limited to patients with clear cell carcinoma or tumors with clear cell components but excluded patients with non-clear cell RCC. Non-clear cell RCC is rare and patients with non-clear cell renal cell carcinoma represent a particularly difficult group. As well, there are a number of patients labelled as non-clear cell carcinoma who in fact harbor clear cell components and thus should be eligible. Non-clear cell renal cell carcinoma includes a variety of histologically and genetically distinct subtypes with papillary, chromophobe, oncocytoma and collecting duct subtypes probably the most common ones. 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.

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Due to the distinct differences between clear cell and non-clear cell RCC, the results of CheckMate-025 are not generalizable to non-clear cell RCC. However, it is expected that PD-1 inhibitors and immunotherapy will have activity in non-clear cell RCC as well and nivolumab should be made available to patients with clear-cell histology. Health Canada approval for Nivolumab was granted for metastatic RCC without specifying a particular subtype.

Patients with performance status 2 or 3 represent a particular problem since almost all randomized RCC studies to date have excluded these patients. However, performance status should not be a criterion to exclude patients from nivolumab therapy. Real world data with tyrosine kinase inibitors such as sunitinib have shown a good benefit for TKIs even in patients with performance status 2 or 3 although these patients were initially excluded from the pivotal studies. There is no biologic reason why patients with performance status > 1 should respond differently to nivolumab. In contrast to TKIs or mTOR inhibitors, Nivolumab is very well tolerated, which will safely allow treatment for patients with performance status > 1. In a subset analysis of this trial, nivolumab actually was associated with higher OS benefit in patients with poor-risk disease (HR=0.47; 95% CI 0.30 to 0.73). This is consistent with data from other studies showing good results in patients with sarcomatoid differentiation that is generally associated with more aggressive RCC.

Checkmate-025 permitted 1 or 2 prior TKI therapies. However, given the completely different mechanism of action of nivolumab compared to targeted agents there is no reason why patients with more than 2 prior lines of targeted therapies should not respond to nivolumab. In fact, significant activity was seen in earlier studies which included patients with multiple lines of prior therapy.[12,13] Given the activity of nivolumab it is expected that nivolumab will rapidly become the standard in second-line and will therefore make the question of activity after several lines of targeted therapies quickly irrelevant.

As with every randomized study in metastatic RCC in the targeted therapy era, patients with brain metastases were excluded from the study. The reasons for the exclusion are two-fold. Patients with brain metastases carry a worse prognosis and have a higher risk of bleeding in these metastases if not properly treated e.g. with radiation. While brain metastases are a negative prognostic factor and these patients do worse than patients without brain metastases, real world data with TKis and mTOR inhibitors have demonstrated a benefit even for these patients.[14] Today in clinical practice, patients with brain metastases are treated the same way as patients without brain metastases. Therefore patients with brain metastases should not be excluded from treatment with nivolumab.

The results of this trial are not generalizable to the first-line situation. Randomized trials in the first-line setting are currently ongoing and will determine the value of immunotherapy in the first-line setting.

Treatment options after nivolumab are an important issue which has also been recognized by the patient advocacy group. In the nivolumab group 227 of the 410 patients (55%) and 260 of the 411 patients (63%) in the everolimus group received subsequent systemic therapy. The most common therapeutic agents used after treatment with nivolumab were everolimus (105 patients, 26%), axitinib (99 patients, 24%), and pazopanib (37 patients, 9%); the most common agents used after treatment with everolimus were axitinib (149 patients, 36%), pazopanib (64 patients, 16%), and sorafenib (38 patients, 9%). The exact impact of subsequent therapies in the current study is being examined and has yet to be published. However, all of these therapies may have contributed to the benefit seen in the nivolumab arm. In addition, both studies, RECORD-1 examining everolimus versus placebo and AXIS, investigating axitinib versus sorafenib included patients with prior immunotherapy (mainly high-dose interleukin and interferon) and recent additional retrospective data indicate good activity of targeted agents after immunotherapy.[20] It is expected that

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everolimus and axitinib (if not given prior to nivolumab) will be moved to later lines of therapy as in the checkmate-025 study and should therefore be permitted after nivolumab**.**

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to nivolumab in the second-line / third-line treatment of advanced and metastatic RCC based on one high-quality randomized controlled trial that demonstrated a clinically meaningful and statistically significant benefit in overall survival for nivolumab compared with everolimus. This was based on CheckMate 025 which supports the use of nivolumab after one or two prior TKIs in patients with clear cell or clear cell component carcinoma. Nivolumab should therefore replace everolimus in the second-line setting after prior anti-angiogenic therapy. Based on previous experience with TKis, the excellent tolerability of nivolumab and the high unmet need for these patients, performance status > 1 or the presence of brain metastases should not exclude patients from nivolumab treatment.

In making this recommendation, the Clinical Guidance Panel considered:

- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC presents with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC who have failed first-line therapy. Everolimus and axitinib are the only drugs available. Both agents were approved based on a PFS benefit and both drugs are associated with a number of substantial side effects, including hypertension, fatigue, diarrhea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes. Hence there is an urgent need for better treatment options in RCC.
- Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that PD-1 inhibitors and immunotherapy will have activity in non-clear cell RCC. Nivolumab should therefore be made available to patients with non-clear-cell histology.
- In contrast to TKIs or mTOR inhibitors, nivolumab is very well tolerated, which will safely allow treatment for patients with performance status > 1. This is consistent with current clinical practice where patients with performance status 2 or 3 are treated with tyrosine kinase inhibitors such as sunitinib and have shown a good benefit even in although these patients were initially excluded from the pivotal studies.
- Given the completely different mechanism of action of nivolumab compared to targeted agents there is no reason why patients with more than 2 prior lines of targeted therapies should not respond to nivolumab. It is however expected that nivolumab will rapidly become the standard in second-line and will therefore make the question of activity after several lines of targeted therapies quickly irrelevant.
- In clinical practice, patients with brain metastases are treated the same way as patients without brain metastases. Therefore patients with brain metastases should not be excluded from treatment with nivolumab.
- The results of this trial are not generalizable to the first-line situation and should await randomized trials in the first-line setting which are currently ongoing.
- It is of utmost importance to recognize pseudoprogression in order to not stop an active therapy in RCC patients. Checkmate-025 accounted for this phenomena by permitting treatment beyond progression. True progression was defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

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3 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.

3.1 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2015, there were 6200 new cases and 1,800 deaths due to the disease.[5] About 90% 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, sarcomatoid, 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. Of the patients diagnosed with localized disease, 30-50% 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.[2]

Metastatic RCC is considered refractory to both conventional cytotoxic chemotherapy and conventional radiation therapy. Historically, immunotherapy (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.[21-23] 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 Heng criteria which better reflects treatment with targeted agents has come into regular use and for the purposes of clinical trials.[24-26]

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).[27] 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.

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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.

3.2 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 adjuvant or neoadjuvant therapy although we are currently awaiting more results of large adjuvant studies

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 for patients with metastatic clear-cell RCC. Although these agents were helpful for a small group 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 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.[28]

There are currently three different classes of agents in clinical use for the treatment of metastatic clear-cell RCC: small molecule tyrosine kinase inhibitors (TKIs) such as sunitinib or 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 signaling, 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.[16,17] 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. Temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria.[29]

Second Line

After failure of tyrosine kinase inhibitor first-line therapy, everolimus, an oral mTOR inhibitor as well as axitinib, a VEGFR-TKI are considered standard second line treatment options.[3,4,6,30] Both drugs were approved based on a progression-free survival benefit,

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which was the primary endpoint of both pivotal studies. Everolimus has demonstrated a significant PFS benefit (4.9 versus 1.9 months; HR 0.32) in a randomized phase III trial (RECORD-1) which compared everolimus to placebo in patients with failure of at least one prior line of TKI therapy.[6] Axitinib showed a PFS benefit over sorafenib in patients who had previously failed a TKI treatment with median PFS of 6.7 versus 4.7 months (HR 0.67) in the overall group and 4.8 versus 3.4 months (HR 0.74) in sunitinib pretreated patients (AXIS trial). None of these studies was a pure second-line trial, and both studies allowed enrolment of patients who had been treated with immunotherapy treatment (interferon, interleukin-2) in addition to a VEGFR-TKI.

Neither of these studies demonstrated a clear overall survival benefit. In the axitinib study, median overall survival was 20.1 months with axitinib and 19.2 months with sorafenib (HR 0.97). The RECORD-1 study was designed as a cross-over trial resulting in a similar, not statistically different median overall survival of 14.8 versus 14.4 months (HR 0.87). The use of both tyrosine kinase inhibitors and mTOR inhibitors is also limited by their toxicity which includes fatigue, hand-foot syndrome, hypertension, hypothyroidism, diarrhea, and mucositis, skin rash and pneumonits as the clinically most relevant. Hence, the development of new treatment options which prolong overall survival while being well tolerated remains a high priority.

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively 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. Interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of the cellular immune response. Interruption of the interaction of PD-1 and PD-L1 leads to antitumor response via activation of an immune response.

Nivolumab represents therapy with a completely novel mechanism of action and was randomized against everolimus in a large open-label phase III study including 821 patients (Checkmate-025) (Motzer et al NEJM 2015).

Several important findings should be mentioned:

A lack of predictive value for PD-L1 expression has been observed in other tumor types while in some tumors PD-L1 expression appears to be somewhat predictive of a tumor response e.g. in bladder cancer. Recent data in RCC and lung cancer suggest significant intrapatient heterogeneity of PD-L1 expression with discordant expression of PD-L1 between primary tumor and metastases and variable expression even among metastases making the exact measurement of PD-L1 and subsequent development of PD-L1 expression as a predictive biomarker challenging.[31] In addition, there appears to exist prominent interassay variability or discordance among different antibodies used for measurement of PD-L1 expression.[19] This could be due to different antibody affinities, limited specificity, or distinct target epitopes and makes the proper choice of antibody difficult.

Nivolumab represents therapy with a completely novel mechanism of action and was randomized against everolimus in a large open-label phase III study including 821 patients (Checkmate-025). This is the first randomized study in the second-line setting of metastatic kidney cancer with a clear overall survival benefit and is the focus of this report.

An important phenomenon associated with immunotherapy in RCC and already known from melanoma therapy is pseudoprogression.[32] Across the immunotherapy clinical trial program for melanoma, four patterns of response to ipilimumab therapy in patients with advanced melanoma were observed. Two of the response patterns are captured with conventional

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RECIST 1.1 response criteria while the other 2 would be assessed as progressive disease according to RECIST 1.1: (a) response in baseline lesions-evident by week 12, with no new lesions, and (b) "stable disease" (which in some patients may be followed by a slow, steady decline in total tumor burden). The other two response patterns are relatively new and associated with immunotherapy: (c) responses after an initial increase in total tumor burden ("pseudoprogression") and (d) a reduction in total tumor burden during or after the appearance of new lesion(s) at time points later than week 12 ("pseudoprogression"). New, immune-related response criteria have been developed in order to account for these unusual response behavior.[32] However studies are currently ongoing to better characterize this phenomenon. In melanoma patients this phenomenon has been described in up to 15-20% of patients.[33] Since both studies, RECORD-1 examining everolimus versus placebo and AXIS, investigating axitnib versus sorafenib included patients with prior immunotherapy and recent data indicate good activity of targeted agents after immunotherapy it is expected that everolimus (and axitinib if not given prior to nivolumab) will be moved to later lines of therapy as in the checkmate-025 study.

3.3 Evidence-Based Considerations for a Funding Population

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

Metastatic or advanced, inoperable renal cell carcinoma

Clear cell histology or clear cell component

Failure of one or two prior TKIs.

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

3.4 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.

Nivolumab has been approved by Health Canada for the treatment of melanoma. Nivolumab has demonstrated activity in lung cancer, some GI malignancies and other tumor types in earlier studies.

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4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient advocacy groups are invited to provide input on drug reviews to ensure patients' experiences of living with cancer and undergoing treatment are routinely considered as part of the pCODR Review Process. The patient advocacy groups are independent of pCODR. The following patient advocacy group provided input on nivolumab (Opdivo) for the treatment of metastatic or advanced renal cell carcinoma at the beginning of the review process and their input is summarized below:

Please see below for a summary of specific input received from the patient advocacy group (Kidney Cancer Canada).

Kidney Cancer Canada conducted an online survey of patients and caregivers from January 5 to January 29, 2016 to assess the challenges patients and caregivers face as a result of the disease and to gain insight into their experiences with therapies used to treat kidney cancer, in particular the treatment under review – nivolumab. A total of 139 respondents completed the survey: 124 (89%) respondents were from across Canada representing 9 provinces and 1 territory (no responses from Newfoundland, Northwest Territories or Nunavut), 14 respondents were from the US and 1 respondents was from Australia. A total of 63 (45%) respondents were living with kidney cancer, 43 (31%) respondents were kidney cancer survivors, and 33 (24%) respondents were caregivers. A total of 17 respondents indicated that they had used nivolumab to treat their kidney cancer, 10 of whom were from Canada and seven (7) of whom were from the US. A total of 10 respondents used nivolumab monotherapy and seven (7) respondents used nivolumab in combination with another therapy. With regards to duration of therapy, nine (9) were treated with nivolumab from 1 to 6 months, five (5) respondents were treated with nivolumab for 7 to 12 months, one (1) respondent was treated with nivolumab for 1 to 2 years, and two (2) respondents were treated with nivolumab for more than 2 years. Among these respondents who have experience with nivolumab, two are no longer on treatment.

From a patient's perspective, pain and mobility were ranked the highest in terms of aspects of kidney cancer important to control, followed by fatigue and shortness of breath. Respondents indicated that these symptoms impact on their day-to-day activities, including their ability to work, travel, exercise, conduct household chores, fulfill family obligations and ability to spend time with family and friends. Drug therapies used to treat kidney cancer (other than nivolumab) included sunitinib, pazopanib, everolimus, axitinib, high dose interleukin 2, sorafenib, temsirolimus, bevacizumab in combination with erlotinib, bevacizumab in combination with CRLX101, savolitinib, carboplatin & gemcitabine, and clinical trial drug. The most common side effects experienced from these treatments were fatigue, followed by diarrhea and loss of appetite.

According to Kidney Cancer Canada, respondents who have not used nivolumab expect that this therapy would provide for long-term stability or reduction of disease; improvement to physical condition such as decreasing the size of or stabilizing the tumour, reducing pain, improving breathing. Respondents also stated that improvement to quality of life were extremely important if they were to consider taking a new therapy for their kidney cancer. Respondents who have experience with nivolumab rated their quality of life as high while on treatment. Overall, 76% of respondents rated side effects of nivolumab as tolerable; these side effects include, fatigue, decreased appetite, and pain in muscles, bones and joints. Kidney Cancer Canada noted that in many cases, a large proportion (>60%) of respondents selected "N/A", suggesting that the following side effects (e.g., diarrhea, nausea, injection-related side-effects at the time of infusion, flu-like symptoms, and hand-foot syndrome) may not apply to them. While these side effects appear to be more tolerable, Kidney Cancer Canada acknowledges that when they do occur it progresses quickly with possible long term negative health outcomes.

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Kidney Cancer Canada highlighted that patients require choice in second-line therapy to continue managing their disease and side effects and to maintain quality of life.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Renal Cell Carcinoma

Patients with kidney cancer may experience many symptoms. Kidney Cancer Canada asked respondents to rate on a scale of 1-5 (where 1 = not important and 5 = very important), how important it is to control various aspects of kidney cancer. Pain and mobility were ranked the highest, which was very important (for 67% and 56% of respondents respectively), followed by fatigue and then shortness of breath. The results collected from the respondents are reproduced below. Other reported aspects of kidney cancer important to control were depression, heartburn, high blood pressure and lack of appetite.

Table 1.

How important it is to control various aspects of kidney cancer? Respondents rated on a scale of 1-5.							
	1 - Not important	2	3	4	5 - Very important	N/A	Total
Pain	6.96% 8	2.61% 3	4.35% 5	17.39% 20	66.96% 77	1.74% 2	115
Mobility	2.63% 3	2.63% 3	7.02% 8	28.95% 33	56.14% 64	2.63% 3	114
Fatigue	0.86% 1	4.31% 5	14.66% 17	31.90% 37	44.83% 52	3.45% 4	116
Shortness of Breath	4.35% 5	5.22% 6	7.83% 9	26.09% 30	47.83% 55	8.70% 10	115

Kidney Cancer Canada also asked respondents to rate on a scale of 1-5 (where 1 = not at all and 5 = significant impact), how symptoms associated with kidney cancer impact or limit day-to-day activities. Respondents indicated that their ability to work was the most impacted followed by ability to travel, ability to exercise, ability to conduct household chores, ability to fulfill family obligations and ability to spend time with family and friends. The results collected from the respondents are reproduced in Table 2 below.

Kidney Cancer Canada reported that nine (9) respondents provided a comment under “other”. Two respondents indicated that they had no symptoms and two respondents indicated that they were stable for now. Other individual responses included: affects eating and restricted from doing many things, financial impact and unable to contribute to community.

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Table 2.

How do symptoms associated with kidney cancer impact or limit your day-to-day activities? Respondents rated on a scale of 1-5.							
	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Ability to work	21.74% 25	10.43% 12	15.65% 18	13.04% 15	30.43% 35	8.70% 10	115
Ability to travel	18.26% 21	20.00% 23	18.26% 21	18.26% 21	21.74% 25	3.48% 4	115
Ability to exercise	21.74% 25	14.78% 17	20.87% 24	23.48% 27	17.39% 20	1.74% 2	115
Ability to conduct household chores	25.44% 29	17.54% 20	26.32% 30	20.18% 23	8.77% 10	1.75% 2	114
Ability to fulfill family obligations	26.09% 30	25.22% 29	20.00% 23	11.30% 13	14.78% 17	2.61% 3	115
Ability to spend time with family and friends	28.70% 33	24.35% 28	20.00% 23	11.30% 13	13.04% 15	2.61% 3	115

Kidney Cancer Canada provided a quote from a caregiver respondent to help illustrate the impact on day-to-day activities: "*This disease has changed (X) life. He is almost immobile and I have had to take on duties with our kids and home that he used to be able to do. Emotionally it is exhausting on our family. My children have only remembered (XXX) sleeping on the couch and feeling sick. They were 3 and 6 when he was diagnosed. Nobody should have to feel like this. Many times where he did not want to fight anymore. He doesn't miss a day of work. When he wanted to call it quits at a few points I knew how bad it was. Strongest man I know to get through it! These patients need help. It takes a horrible tole on a family.*"

4.1.2 Patients' Experiences with Current Therapy for Renal Cell Carcinoma

Kidney Cancer Canada asked in a closed ended question if respondents have used any drug therapy to treat their kidney cancer. A total of 74 (63%) of respondents indicated "yes", 32 (27%) respondents indicated "no" and 8 (7%) respondents indicated "not yet" and 4 (3%) respondents indicated "I'm not sure". Both "no" and "not yet" may be interpreted as the respondent has not used therapy to treat their kidney cancer. Therapies selected by respondents from a list provided by Kidney Cancer Canada other than nivolumab are reproduced in Table 3 below.

Additional treatments indicated by respondents under "other" were: bevacizumab in combination with erlotinib (n=2), bevacizumab in combination with CRLX101 (n=1), savolitinib (n=1), carboplatin & gemcitabine (n=1), clinical trial drug (n=4).

Table 3.

Drug therapies used to treat kidney cancer	Number of respondents (%) Total number of respondents = 68
Sutent™ (sunitinib)	48(70.59%)
Votrient™ (pazopanib)	18(26.47%)
Afinitor™ (everolimus)	14(20.59%)
Inlyta™ (axitinib)	14(20.59%)
High Dose Interleukin 2 (HD-IL2)	9(13.24%)
Nexavar™ (sorafenib)	3(4.41%)
Torisel™ (temsirolimus)	2(2.94%)

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According to Kidney Cancer Canada, respondents rated the side effects of the treatments as tolerable. The most common side effects from treatment was fatigue (experienced by 83% of respondents), followed by diarrhea (experienced by 74% of respondents), and loss of appetite (experienced by 64% of respondents). Side effects selected by respondents from a list provided by Kidney Cancer Canada are reproduced in Table 4 below. Additional side effects reported by respondents under "other" included: mouth sores or sensitivity (n=3), taste loss/affected (n=3), acid reflux (n=2), geographic tongue (n=2), hair loss (n=2), high blood pressure (n=2), and palpitations (n=2). Other individual responses included: edema, elevated liver, elevated potassium, extreme colitis, headaches, heart burn, mobility issues, and weight loss.

Table 4.

Side effects experienced from treatment	Number of respondents (%) Total number of respondents = 70
Fatigue	58(82.86%)
Diarrhea	52(74.29%)
Loss of appetite	45(64.29%)
Hand-foot syndrome	35(50.00%)
Skin problems	36(51.43%)
Nausea/Vomiting	31(44.29%)
Shortness of breath	26(37.14%)
Pain	23(32.86%)
Bleeding	12(17.14%)
Fever	11(15.71%)
Pneumonia	8(11.43%)

Kidney Cancer Canada reported a total of 107 respondents out of 115 respondents indicated that it was "very important" to have access to new treatments for kidney cancer. According to Kidney Cancer Canada, 68 respondents expressed that it was "very important" for them and their physician to be able to make a choice of drug(s) based upon each different drug's known side effects.

Among the Canadian respondents that responded to the question (n=61), a total of 33% (n=20) of Canadian respondents indicated that they and/or their physician experienced hardships in accessing therapy for kidney cancer, while 25% (n=15) of Canadian respondents selected "no", 41% (n=25) of Canadian respondents selected "not at this point" and 2% (n=1) of Canadian respondents selected "not sure". Among the 19 Canadian respondents that commented on their challenges or hardship (some of whom noted more than one) 32% (n=6) noted cost/financial issues, 32% (n=6) indicated coverage issues, 21% (n=4) had to travel to the US for treatment, 11% (n=2) had to travel long distances for treatment, 11% (n=2) noted side effects were the challenge, 5% (n=1) commented on lack of options for treatment, and 5% (n=1) noted access to treatment was a challenge.

Below were reported responses to help illustrate some of the challenges and hardships experienced by the respondents:

- *"Cost to access & long wait for approval which can cause extreme anxiety and excessive stress on the family members."*
- *"Getting approval from our private medical for the drug was very stressful. Without private medical the cost would be prohibited."*
- *"Access to right drug is a challenge. I also have to travel to USA every two weeks as Avastin is not approved for Kidney Cancer in Canada."*

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According to Kidney Cancer Canada, patients and caregivers recognizes that the current second-line treatment options are not effective for everyone and can be difficult to access. Notwithstanding, Kidney Cancer Canada submits that choice in the second-line and access to new and upcoming treatments without restrictions, is important for managing the progression of kidney cancer for patients

4.1.3 Impact of Renal Cell Carcinoma and Current Therapy on Caregivers

Although Kidney Cancer Canada received responses from 33 caregiver respondents, not all respondents replied to all questions. Kidney Cancer Canada asked caregiver respondents to rate on a scale of 1-5 (where 1 = not at all and 5 = significant impact), how do symptoms of kidney cancer impact or limit your day-to-day activity and/or quality of life. According to Kidney Cancer Canada, caregiver respondents suggested that all activities were impacted to a certain extent. Caregiver respondents indicated that their ability to travel was the most impacted followed by ability to work, and then ability to volunteer. The results collected from the respondents are reproduced in Table 5 below.

Table 5.

How do symptoms of kidney cancer impact or limit your day-to-day activity and/or quality of life? Caregiver respondents rated on a scale of 1-5.							
	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Ability to travel	8.33% 2	8.33% 2	12.50% 3	8.33% 2	62.50% 15	0.00% 0	24
Ability to work	16.67% 4	8.33% 2	16.67% 4	12.50% 3	41.67% 10	4.17% 1	24
Ability to volunteer	25.00% 6	4.17% 1	12.50% 3	12.50% 3	37.50% 9	8.33% 2	24
Ability spend time with family & friends	16.67% 4	16.67% 4	20.83% 5	20.83% 5	25.00% 6	0.00% 0	24
Ability to exercise	25.00% 6	25.00% 6	16.67% 4	8.33% 2	25.00% 6	0.00% 0	24
Ability to fulfill family obligations	29.17% 7	16.67% 4	29.17% 7	12.50% 3	12.50% 3	0.00% 0	24
Ability to conduct household chores	33.33% 8	33.33% 8	20.83% 5	8.33% 2	4.17% 1	0.00% 0	24

Caregiver respondents were asked, "*Do you or have you previously faced challenges because of the side effects of the kidney cancer drugs*?" Of the caregiver respondents that answered the question (n=24), a total of 58% (n=14) of caregiver respondents indicated that they faced challenges because of the side effects of the kidney cancer drugs, while 12% (n=3) caregiver respondents responded "no" and 29% (n=7) caregiver respondents selected that the question did not apply because the patient has not been treated with kidney cancer drugs. 10 caregiver respondents also described the types of challenges they faced because of the side effects of the drugs. These challenges included: stressful dealing with patient side effects 50% (n=5), disruptive to daily life including missed work 30% (n=3), must tend to patient medical needs 20% (n=2), financial stress 10% (1), loss of sleep 10% (n=1), and manage medications to treat side effects 19% (n=1).

Below were reported responses from caregiver respondents to help illustrate some of the impacts on day-to-day activity and/or quality of life:

- *"Constant challenge to address symptoms and change medication or reduce dosages and deal with fatigue or what is causing what!!"*

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- *"Multiple adjustments: from dietary to life style change, impact on income list is long"*
- *"severe hypertension and postural hypotension required my to be close by 24/7 During episodes of severe pain I slept very little to be sure my mother had her pain meds every 4 hours."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Nivolumab

Kidney Cancer Canada asked respondents to rate on a scale of 1-5 (where 1 = not important and 5 = extremely), how important various outcomes would be to them if they were to consider taking a new therapy for their kidney cancer. According to Kidney Cancer Canada, all aspects were extremely important. Chance for long-term stability or reduction of disease was ranked the highest, followed by improvement to physical condition such as decreasing the size of or stabilizing the tumour, reducing pain, improving breathing; and then improvement to quality of life. The results collected from the respondents are reproduced in Table 6 below.

Table 6.

How important would various outcomes be if you were to consider taking a new therapy your kidney cancer? Respondents rated on a scale of 1-5.							
	1 - Not important	2	3	4	5 - Extremely important	N/A	Total
Chance for long-term stability or reduction of disease.	0.00% 0	0.00% 0	2.20% 2	2.20% 2	95.60% 87	0.00% 0	91
Improvement to your physical condition such as decreasing the size of or stabilizing the tumour, reducing pain, improving your breathing.	0.00% 0	0.00% 0	2.20% 2	4.40% 4	92.31% 84	1.10% 1	91
Improvement to your quality of life.	1.10% 1	0.00% 0	3.30% 3	12.09% 11	82.42% 75	1.10% 1	91

Kidney Cancer Canada asked respondents to rate on a scale of 1-5 (where 1 = no side effects and 5 = significant side effects), the severity of side effects (e.g., nausea, fatigue, vomiting, diarrhea, shortness of breath) they would be willing to tolerate if they were to consider taking a "new therapy proven to be effective". According to Kidney Cancer Canada, 91 respondents indicated that they were more willing to accept side effects.

A total of 17 survey respondents indicated that they had used nivolumab to treat their kidney cancer; 10 respondents used nivolumab monotherapy and seven (7) respondents used nivolumab in combination with another therapy.

In terms of duration of therapy, nine (9) respondents were treated with nivolumab from 1 to 6 months, five (5) respondents were treated with nivolumab for 7 to 12 months, one (1) respondent was treated with nivolumab for 1 to 2 years, and two (2) respondents were treated with nivolumab for- more than 2 years. Among these respondents, two (2) respondents are no longer on treatment.

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Kidney Cancer Canada noted that not all 17 respondents provided an answer to each question. For instance when asked to rate the effectiveness nivolumab in controlling kidney cancer on a scale of 1-5 (where 1 = not effective and 5 = extremely effective), a total of 5 patients (30%) selected N/A. A total of 6 respondents (35%) rated it a 5, 4 respondents (24%) rated it a 4 and 2 respondents (12%) rated it a 3.

Kidney Cancer Canada asked respondents to rate overall, the side effects of nivolumab on a scale of 1-5 (where 1 = completely intolerable and 5 = very tolerable. Please see the results reproduced in Table 7 below. A total of 13 (76%) out of 17 respondents rated side effects of nivolumab as very tolerable. Respondents were also asked to rate each side effect of nivolumab on a scale of 1-5 (where 1 = completely intolerable and 5 = very tolerable). Kidney Cancer Canada noted that in many cases, a large proportion of respondents selected "N/A", suggesting that the side effect may not apply to them. One respondent noted *"Extreme Colitis"*.

Table 7.

Rate each side effect of nivolumab on a scale of 1-5							
	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Diarrhea	7.69% 1	7.69% 1	0.00% 0	7.69% 1	15.38% 2	61.54% 8	13
Headache	8.33% 1	0.00% 0	8.33% 1	16.67% 2	16.67% 2	50.00% 6	12
Shortness of breath	0.00% 0	7.69% 1	23.08% 3	7.69% 1	30.77% 4	30.77% 4	13
Nausea	0.00% 0	7.69% 1	0.00% 0	15.38% 2	15.38% 2	61.54% 8	13
Rash	0.00% 0	0.00% 0	21.43% 3	14.29% 2	28.57% 4	35.71% 5	14
Pain in muscles, bones and joints	6.67% 1	0.00% 0	6.67% 1	33.33% 5	40.00% 6	13.33% 2	15
Constipation	0.00% 0	7.14% 1	0.00% 0	21.43% 3	28.57% 4	42.86% 6	14
Injection-related side-effects at the time of infusion	0.00% 0	0.00% 0	8.33% 1	8.33% 1	16.67% 2	66.67% 8	12
Fatigue	0.00% 0	0.00% 0	14.29% 2	35.71% 5	42.86% 6	7.14% 1	14
Decreased appetite	0.00% 0	0.00% 0	7.14% 1	14.29% 2	50.00% 7	28.57% 4	14
Cough	0.00% 0	0.00% 0	0.00% 0	15.38% 2	30.77% 4	53.85% 7	13
Flu-like symptoms	0.00% 0	0.00% 0	0.00% 0	8.33% 1	25.00% 3	66.67% 8	12
Hand-foot syndrome	0.00% 0	0.00% 0	0.00% 0	0.00% 0	25.00% 3	75.00% 9	12

In addition, respondents were asked to rate the side effects of nivolumab compared to other treatments for kidney cancer. The results collected from the respondents are reproduced in Table 8 below. Four respondents also provided additional comments. Two respondents expressed that IL-2 was much easier, and one respondent noted that "*Carbo & gemzar, easier to tolerate*". One respondent could not answer "*as I was taking Sutent and Optivo in tandem*".

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Table 8.

Rate the side effects of nivolumab compared to other treatments for kidney cancer.							
	1 - Much harder to tolerate	2	3	4	5 - Much easier to tolerate	N/A	Total
Nexavar™ (sorafenib)	0.00% 0	0.00% 0	0.00% 0	0.00% 0	25.00% 1	75.00% 3	4
Sutent™ (sunitinib)	0.00% 0	0.00% 0	10.00% 1	0.00% 0	70.00% 7	20.00% 2	10
Torisel™ (temsirolimus)	0.00% 0	0.00% 0	0.00% 0	0.00% 0	25.00% 1	75.00% 3	4
Afinitor™ (everolimus)	0.00% 0	20.00% 1	0.00% 0	0.00% 0	40.00% 2	40.00% 2	5
Votrient™ (pazopanib)	0.00% 0	0.00% 0	20.00% 1	20.00% 1	20.00% 1	40.00% 2	5
Inlyta™ (axitinib)	0.00% 0	0.00% 0	0.00% 0	16.67% 1	33.33% 2	50.00% 3	6

According to Kidney Cancer Canada, respondents (n=15) rated their quality of life as high while taking nivolumab.

Respondents also provided additional comments on their experience with nivolumab:

- *"Since starting nivolumab my scans show no new grow Disease is said to be stable."*
- *"Causes inflammation of cancer sites. Very troubling until I realized that it is a good thing. It means it's working!"*
- *"I cannot say for sure but since most of the sides effects I experienced are commonly attributed to taking Sutent it is possible the taking of Optivo was tolerable for me."*
- *"It is not a completely forward path, I have had shrinkage, stable disease, some growth, then stable disease again. All worth it!"*
- *"everyone's experience is very different"*
- *"Most easily tolerated drug I've been on. Also excellent results to date."*

When asked how has nivolumab changed, or how is it expected to change your long-term health and well-being, a total of 10 respondents provided an answer to the open-ended question. Below were reported responses to help illustrate experiences and expectations for nivolumab:

- *"I feel it will extend my life expectancy"*
- *"We are expecting a good response; too early to scan."*
- *"Been stable with some shrinkage for almost a year, hoping for long term stability."*
- *"Hoping to reduce the cancer cells"*
- *"Will allow me to live longer with higher quality of life"*
- *"I am very pleased with how I have handled being on Opdivo for 9 mo. Worked through side effects with help with Dr XXX"*
- *"I am hoping to live longer and to get to NED"*
- *"Tumours (metastasized to lungs) are no longer visible"*
- *"It has slowed thr growth of the nodules"*

Kidney Cancer Canada asked respondents to share their story and why access to nivolumab and

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future therapies are important. A total 11 respondents who have used nivolumab provided comments. According to Kidney Cancer Canada, although responses varied, many respondents commented on the importance of extending life, and some respondents commented on the considerable benefit of nivolumab.

- *"Stage IV renal cell carcinoma. Since on Opdivo most of my tumors have completely shrunk or are stable. I continue to work full time and enjoy life."*
- *"I was on Sutent for 3 years, well above the average time a patient normally takes it. It was effective but my cancer was beginning to grow so I was eligible for a clinical trial with Opdivo. I'm hopeful it will be an effective treatment and excited about the fact that side effects will be minimal/non-existent. Currently there are not a lot of treatments for Kidney Cancer so new therapies are extremely important to me."*
- *"Like many people this took us by surprise. Our research showed treatment is just recently showing promising results. Even though it is a fairly common cancer little has been done compared to higher profile cancers. We are fortunate to have a dr that immediately offered a clinical trial that included Nivo. Unfortunately the clinical trial was no longer an option due to side effect of extreme colitis, but without a doubt it responsible for successful outcome (so far) with the reduction of tumours. It is very frustrating to know that Nivo is available in other countries like the US but not attainable here in Canada."*
- *"I was diagnose with kidney cancer in 2004. Right kidney removed. I was followed with CT scans, 2009 something on my pancreas, biopsy said it wasn't cancer. 2011 it was back surgery on head of pancreas, not clear margins. 2014 spots on liver and left kidney. Since start clinical trail disease has been stable."*
- *"I had previously had surgery to remove my right kidney. Soon afterwards I also had a spot ablated from my remaining kidney. I also had a subsequent surgery to remove the rest of the redundant right ureter as it was deemed to have a cancerous lesion. Imaging results approximately 6 months after this surgery revealed additional lesion in my kidney, pancreas and chest wall. At this time I was referred by my urologist to an oncologist. The oncologist determined I was a good candidate for a clinical trial that was still recruiting so I agreed to participate. In February 2013 I began the trial taking Sutent and Optivio simultaneously. In June of 2015, in consultation with my oncologist, I ceased the therapy. Recent imaging had shown all tumours in my abdominal area had disappeared and the one in my chest wall had shrunk considerably and it was undetermined what the status of the remaining pot was. At this point, after 2.5 years of taking the drugs I was very fatigued from the side effects and rigours of the treatment schedule. As of December 2015 my situation has remained stable and I continue to go for imaging and follow ups every 3 months."*
- *"we have few options with real progression free survival benefit. Those who have responded to Opdivo have had some overwhelming responses. Over time, I've been told, the side effects lessen if you are adequately supported through the initial difficulties."*
- *"63 you male, left radical nephrectomy in 2013, recently retired. This drug either alone or as a combo seems to be a MRCC patients best option. High Q of,L with tolerable side effects is a major issue."*
- *"It is so important to be seen by a renal oncologist and I have found the best in Dr. XX in XX. It is worth us travelling to XX from XX every two weeks. We mostly drive and occasionally fly. Renal cancer is one of the most treatable if surgery works and one of most difficult to treat if it metastasized. We need access in every province to the newest and most promising treatments. I did not want to try current standard of care & wait for it to fail as they all do before I got to try Opdivo. Therefore that is why we sought a clinical trial and almost felt we would have to travel to USA to access a trial."*

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- *"I have been on BMS 936558 for four and a half years now. I just finished round 77. Have been on three other trials, with limited success. There is still growth on this drug, but the growth is slow in the progress. It's important because I'm still alive. And by me doing this trial others now have hope to as I have been on it so long."*

4.3 Additional Information

Kidney Cancer Canada recommend that the manufacturer provide a comprehensive training program for doctors and education package for patients. While side effects appear to be more tolerable and less frequent, when they do occur it progresses quickly with possible long term negative health outcomes. Having patients & doctors trained to identify and manage these side effects will improve the overall outcome of this treatment.

According to Kidney Cancer Canada, nivolumab is the only immuno-oncology (IO) treatment option for kidney cancer patients, with other similar treatment options years away in development. Kidney Cancer Canada stated that current treatments have proven to shrink tumours and delay progression in some patients, and felt that adding IO as a treatment option in the second line and beyond would enable patients and doctors to have individualized treatment plans to better control their disease and maintain a high quality of life. Kidney Cancer Canada also indicated that IO will also address an unmet need for treatment options in the third line.

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5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group at the beginning of the review as factors that potentially affect the feasibility of implementing a funding recommendation for nivolumab (Opdivo) for renal cell carcinoma. 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 (www.pcodr.ca).

Overall Summary

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

Clinical factors:

- Indication creep into first line setting
- Unknown treatment duration

Economic factors:

- Drug wastage
- Frequency of administration and clinic visits
- Intravenous treatment where oral treatments are currently available

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

Everolimus is the standard of care for previously treated metastatic renal cell carcinoma. Other treatments include axitinib, pazopanib, sorafenib, sunitinb and temsirolimus.

PAG noted that nivolumab is a new class of therapy for renal cell carcinoma and appears to be better tolerated than everolimus.

5.2 Factors Related to Patient Population

There is a small number of patients with renal cancer relative to other solid tumours.

PAG noted that the funding request does not specify the histologic type of renal cell carcinoma and does not specify the types of previous treatments. However, trials enrolled patients with histologic confirmed clear cell carcinoma and excluded patients previously treated with temsirolimus. PAG is seeking clarity on the patient population who would be eligible for treatment with nivolumab.

PAG indicated that there may be interest from clinicians and patients to use nivolumab in the first-line setting but recognize this would be out of scope of this review.

Nivolumab may be given to patients who have received one, two or three previous treatments and current treatments used in second-line and third-line could be pushed to third-line and fourth-line. PAG is seeking information on the sequencing of current treatments, before and after nivolumab. In addition, PAG noted that axitinib is currently funded only for the second line treatment of mRCC and is seeking information on the appropriate place of treatment with nivolumab.

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Given the many treatments are available and possibly more upcoming new treatments, PAG is seeking guidance from tumour groups for a national treatment algorithm for renal cell carcinoma and sequencing of treatments.

5.3 Factors Related to Dosing

PAG identified that nivolumab is an intravenous infusion administered every 2 weeks, whereas the current standard of care is an oral drug that is administered in the community.

5.4 Factors Related to Implementation Costs

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there could only be one patient in the day. Dose is based on weight and there are two vial sizes available to help address drug wastage. However, any unused portion would be discarded as the stability of reconstituted drug is poor.

Nivolumab is a new class of drug for renal cancer treatment and health care professionals would need to become familiar with the preparation, administration and monitoring upon implementation.

The unknown treatment duration is also a factor since nivolumab is administered until progression, which ranged from 1 to 48 months in the trial.

5.5 Factors Related to Health System

Nivolumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded (i.e. no co-payments for patients) in all jurisdictions for eligible patients, which is an enabler for patients.

As nivolumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer nivolumab or treat serious adverse events. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer nivolumab.

5.6 Factors Related to Manufacturer

The high cost and large potential budget impact of nivolumab will be barriers to implementation.

PAG is seeking information on access of nivolumab through the compassionate program for first-line treatment of renal cell carcinoma and other tumour sites.

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6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of nivolumab (Opdivo) monotherapy for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior systemic therapy

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.

Table 6.1 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
RCTs (published and unpublished)	Patients with inoperable or metastatic renal cell carcinoma who have received prior systemic therapy Subgroups: • Level of PD-L1 expression • Cancer subtypes	Nivolumab monotherapy at the dose of 3mg/kg administered intravenously over 60 minutes every 2 weeks	Second line therapy: • Everolimus; or • Axitinib Third line therapy: • Everolimus	• Overall survival • Progression free survival • Objective response rates (complete, partial) • Time to response • Duration of response • PD-L1 expression level • **Patient-reported outcomes** • **AEs:** – Treatment related AEs – Serious AEs

AEs= adverse events; kg= kilogram; mg= milligram; MSKCC= Memorial Sloan-Kettering Cancer Center;PD-L1= programmed death-ligand 1; RCT= randomized controlled trial

* *Standard and/or relevant therapies available in Canada*

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6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials (February 2016) via Ovid; 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) 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 2 June 2016.

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. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. 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.

6.2.3 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. One members of the pCODR Methods Team made the final selection of studies to be included in the review.

6.2.4 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.

6.2.5 Data Analysis

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

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6.2.6 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 overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

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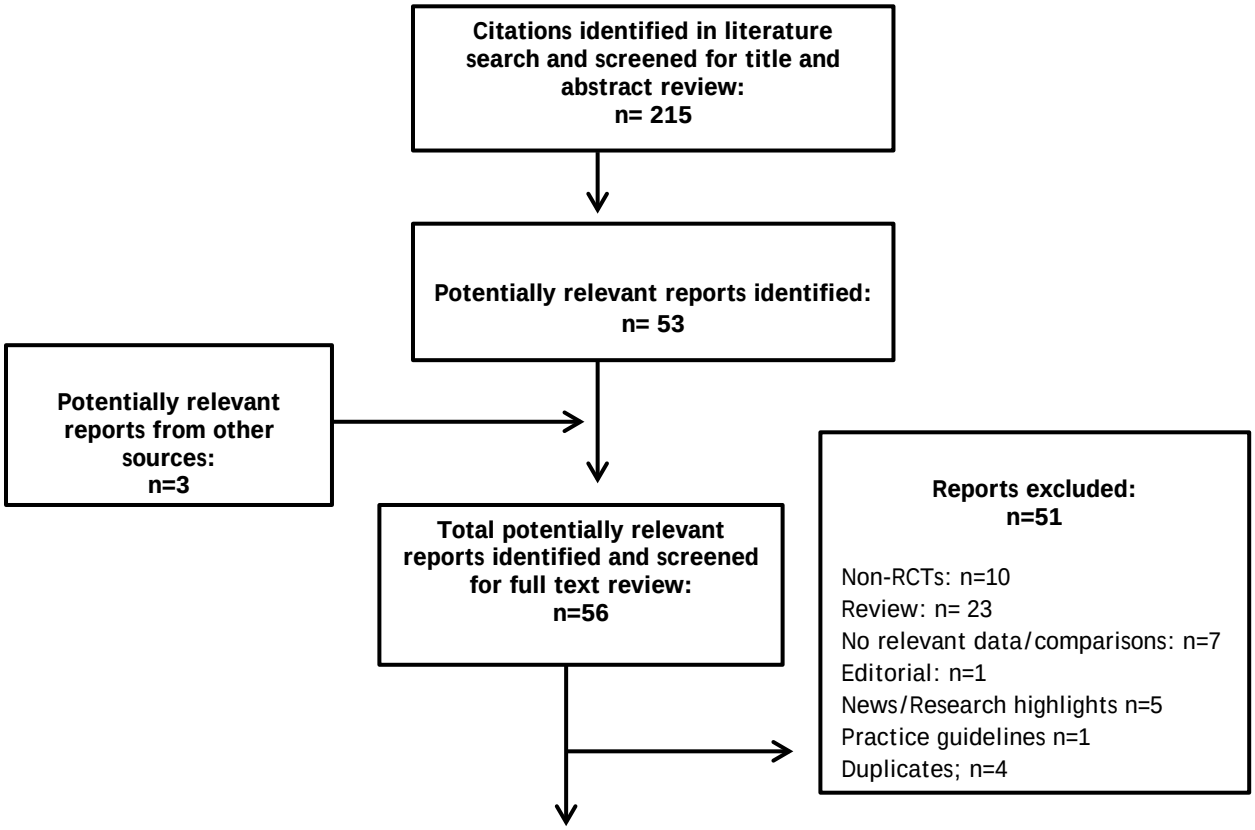
6.3 Results

6.3.1 Literature Search Results

Of the 215 potentially relevant reports identified, one study (CheckMate 25) was included in the pCODR systematic review. Reports were excluded because they were: Reports were excluded because they did not report on outcomes or comparisons of interest; or if they were non-randomized controlled trials, reviews, editorial/news/research highlights, or duplicate publications.

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of studies



Reports presenting data from one randomized controlled trial (n=3) CheckMate 025 Motzer et al (published article)[1] Supplementary data: supplement to Motzer et al (2015)[11] CONSORT diagram: supplement to Motzer et al (2015)[11] Protocol: supplement to Motzer et al (2015)[34] Motzer et al (conference presentation)[8,9] Sharma et al (conference abstract)[10]
Reports identified and included from other sources (n=2) CheckMate 025 Clinical Trials registry information[35] Submission information[36]

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6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 6.2. Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
CheckMate 025[1,8-10] Randomized, open-Label, multicenter, international, phase 3 study Trial number: NCT01668784 CA209-025 Enrollment: October 2012 – March 2014 Randomization: 1:1 ratio, with a block size of 4, stratified based on • geographic regions US, Canada, Western Europe, rest of the world); • MSKCC prognostic risk groups (favourable, intermediate, poor); and • number of previous antiangiogenic treatments (one or two) N randomized= 821 N treated=803 Interim analysis data cut off point date: July 2015 Final data collection date for primary outcome measure (original estimate): May 2015 Study stopped early (end point was met): July 2015. Originally estimated time for end of trial was September 2017. Funded by Bristol Myers Squibb	• Men & women ≥18 years of age • Histologic confirmation of RCC with clear-cell component • Advanced/metastatic RCC • Measurable disease per RECIST 1.1 criteria • Received 1 or 2 prior anti-angiogenic therapy regimens in advanced or metastatic setting • No more than 3 total prior systemic treatment regimens in the advanced or metastatic setting • Evidence of progression on or after last treatment regimen received and within 6 months of enrollment • Karnofsky Performance Score* ≥70% **Exclusion criteria:** • Any CNS metastases or history of CNS metastases • Prior therapy with an Mammalian target of rapamycin (mTOR) inhibitor • Any active known or suspected autoimmune disease • Uncontrolled adrenal insufficiency • Active chronic liver disease • Prior malignancy active within past 3 years, except for locally curable cancers	**Intervention**: Nivolumab 3 mg/kg solution intravenously every 2 weeks **Comparator:** Everolimus 10 mg tablets by mouth daily [both arms: until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study end]	**Primary:** • OS **Secondary:** • PFS • ORR • Duration of ORR • Duration of OS (OS) by Programmed death-ligand 1 (PD-L1) expression levels • Safety (incidence of adverse events, serious adverse events, and laboratory abnormalities) • Disease related symptom progression rate

CNS= central nervous system; **CR**= complete response; **DB**= double-blind; **MSKCC**=Memorial Sloan Kettering Cancer Center; **mTOR**= Mammalian target of rapamycin; **PC**= placebo controlled; **PR**= partial response; **RCC**= renal cell carcinoma; **RCT**= randomized controlled trial; **RECIST**= Response Evaluation Criteria in Solid Tumours; **US**= United States

* Karnofsky Performance Score is a validated measure for quantifying general well-being and the activities of daily life

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a) Trials

One phase III, open-label, multicenter trial (CheckMate 025) was included in this review.[1,8-10] The purpose of the study was to compare the clinical benefit of nivolumab versus everolimus in previously treated patients with advanced or metastatic clear-cell RCC. Adult patients (≥18 years of age) with histologically proven advanced or metastatic RCC and measurable disease based on the Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), who had previously been treated with one or two antiangiogenic treatment regimens, and showed evidence of disease progression within 6 months of enrollment were deemed eligible for inclusion in the study. Other inclusion criteria were no more than three previous systematic treatments for metastatic or advanced RCC and Karnofsky performance status ≥ 70. Patients were excluded if they had metastasis to the central nervous system, any prior therapy with a mammalian target of rapamycin (mTOR) inhibitor, or any medical condition requiring treatment with corticosteroids.[1]

The study randomized 821 eligible patients, in a 1:1 ratio, to receive 3 mg/kg of intravenous nivolumab every 2 weeks or 10 mg of oral everolimus daily until disease progression, unacceptable toxic effects arose, the patient withdrew consent or the study ended. Overall survival (OS) was the primary outcome of the study. The key secondary outcomes included objective response rate (ORR), progression free survival (PFS), safety, and patient reported outcomes (PRO's) using the functional assessment of cancer therapy – kidney symptom index – disease-related symptoms (FSKI-DRS). This questionnaire is composed of nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fevers, and hematuria. Tumor response to the study treatments assessed using computed tomography or magnetic resonance imaging, every 8 weeks for one year, and then every 12 weeks until disease progression or discontinuation of treatment. Safety outcomes (clinical adverse events and laboratory abnormalities) were assessed at each follow up visit. The trial was stopped early, in July 2015, after an independent data monitoring committee confirmed that the study had met the pre-specified threshold for its primary outcome (OS).[1,36]

The study protocol noted accumulating evidence which indicates a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease.[39] Subjects receiving nivolumab were therefore permitted to continue study therapy beyond initial investigator-assessed RECIST 1.1-defined progression as long as patients continued to have clinical benefit with acceptable side effects, according to the investigator's discretion.[1,34] The approved label for everolimus also allowed for continued treatment as long as clinical benefit is observed or until unacceptable toxicity occurs, subjects on the everolimus arm were thus also permitted to continue treatment beyond initial investigator-assessed RECIST 1.1-defined progression if they continued to have clinical benefit with acceptable side effects, according to the investigator's discretion. Subjects were to discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

b) Populations

CheckMate 025 enrolled a total of 821 patients at 146 sites across 24 countries in North America, Europe, Australia, South America, and Asia. The majority of the randomized patients were in US and Canada (42.1%) or Western Europe (34.2%); and only 23.6% of them were recruited from other participating countries.[36]

Patients were randomized to receive nivolumab (n=410) or everolimus (n=411). The randomization was stratified based on study site (US, Canada, Western Europe, rest of the world); Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups (favourable, intermediate, poor); and number of previous antiangiogenic treatments (one or two).

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The baseline demographic and clinical characteristics of the patients were well-balanced between the two study groups (Table 6.3). Details on the baseline patient characteristics are provided in Table 6.3. The patients in both nivolumab and everolimus groups were predominantly white (86% and 89%, respectively) and male (77% and 74%, respectively). The median age was similar (62 years) in both groups, as was the proportion of patients in each MSKCC risk category (Table 6.3). In addition, the majority of patients had received one previous regimen of antiangiogenic treatment for advanced RCC (72%), undergone previous nephrectomy (88%), and had two or more metastatic sites (83%). Lung metastases were the most common site (67%) followed by liver (23%) and bone (18%) metastases. Sunitinib was the most common drug used as the first line treatment in the study participants (59%).

c) Interventions

The CheckMate 025 study intervention was monotherapy with nivolumab, a fully human monoclonal antibody that blocks the immune checkpoint receptor PD-1. The comparator was monotherapy with everolimus, an mTOR inhibitor that has been considered as standard treatment for previously treated advanced and metastatic RCC patients (for more details see section 3.2). Nivolumab was administered intravenously at a dose of 3 mg/kg during 60-minute every 2 weeks. Everolimus was administered orally as a daily dose of 10 mg. The median duration of treatment was 5.5 months (range <0.1 to 29.6) for the nivolumab arm and 3.7 months (range 0.2 to 25.7) for the everolimus arm. The incidence of dose delays was 51% in the nivolumab group (207 of the 406 treated patients) and 66% in the everolimus group (262 of the 397 treated patients). Both study treatments were continued until documented disease progression, unacceptable toxicity, or withdrawal of consent. Dosage adjustment was not allowed for nivolumab but was permitted for everolimus. In the everolimus arm, 26% of the patients had one or more dose reductions.[1]

After the first planned interim analysis, in July 2015, it became clear that nivolumab resulted in a statistically better OS (primary outcome), when compared to everolimus, the trial stopped prematurely, and the eligible patients in the everolimus arm were allowed to cross over to receive nivolumab in an open label extension of the trial.[1,36]

d) Patient Disposition

In the CheckMate 025 trial, patients were randomized to receive nivolumab (n=410) or everolimus (n=411). Four of 410 patients in the nivolumab group and 14 of 411 of those in the everolimus group did not receive the assigned study treatment.[11] Reasons for not being treated with the assigned treatment in the nivolumab group included: not meeting study criteria in 2/4 (50%), withdrawal of consent in 1/4 (25%), and poor compliance in 1/4 (25%). In the everolimus group these reasons included: withdrawal of consent in 8/14 (57%), patient's request to discontinue treatment in 3/14 (22%), disease progression in 1/14 (7%), not meeting study criteria in 1/14 (7%), and other reasons in 1/14 (7%).[11]

At the interim analysis data cut-off date (June 2015), 17% of the patients treated in the nivolumab group (67 of 406) and 7% of those treated in the everolimus group (28 of 397) continued to receive treatment.[11] Among 339 nivolumab-treated patients who discontinued study treatment, 285 (84%) had disease progression, 35 (10%) developed study drug toxicity, 9 (3%) had adverse events (AEs) unrelated to the study drug, 5 patients (1.5%) requested to discontinue treatment, and in 5 (1.5%) the treatment was terminated for other reasons (1.5%). Among the 369 everolimus-treated patients who discontinued treatment, 273 (74%) had disease progression, 53 (14%) developed study drug toxicity, in 14 (4%) patients the treatment was terminated on patient's request, in 11 (3%) for other reasons and in 14 (4%) due to adverse events unrelated to study drug.[11]

All intent-to-treat patient in the nivolumab (n=410) and everolimus (n=411) arms were included in the analysis of efficacy outcomes, while the analysis of safety data was performed on the treated patients (406 in nivolumab and 397 in everolimus arms) only.[11]

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Table 6.3. Baseline patient characteristics of the included studies[1]			
characteristic	Nivolumab (n=410)	Everolimus (n=411)	Total (n=821)
Median age (range) — year	62 (23-88)	62 (18-86)	62 (18-88)
Sex — no. (%)			
Male	315 (77)	304 (74)	619 (75)
Female	95 (23)	107 (26)	202 (25)
Race — no. (%)*			
White	353 (86)	367 (89)	720 (88)
Asian	42 (10)	32 (8)	74 (9)
Black	1 (<1)	4 (1)	5 (1)
Other	14 (3)	8 (2)	22 (3)
MSKCC risk group — no. (%)			
Favorable	145 (35)	148 (36)	293 (36)
Intermediate	201 (49)	203 (49)	404 (49)
Poor	64 (16)	60 (15)	124 (15)
Karnofsky performance status — no. (%)			
<70	2 (<1)	1 (<1)	3 (<1)
70	22 (5)	30 (7)	52 (6)
80	110 (27)	116 (28)	226 (28)
90	150 (37)	130 (32)	280 (34)
100	126 (31)	134 (33)	260 (32)
Disease sites that could be evaluated — no. (%)			
1	68 (17)	71 (17)	139 (17)
≥2	341 (83)	338 (82)	679 (83)
Site of metastasis — no. (%)			
Lung	278 (68)	273 (66)	551 (67)
Liver	100 (24)	87 (21)	187 (23)
Bone	76 (19)	70 (17)	146 (18)
Previous nephrectomy — no. (%)			
Yes	364 (89)	359 (87)	723 (88)
No	46 (11)	52 (13)	98 (12)
Median time from initial diagnosis to randomization (range) — month	31 (1-392)	31 (2-372)	31 (1-392)
Previous antiangiogenic regimens for treatment of advanced renal-cell carcinoma — no. (%)			
1	294 (72)	297 (72)	591 (72)
2	116 (28)	114 (28)	230 (28)
Previous systemic cancer therapy for metastatic renal-cell carcinoma — no. (%)			
Sunitinib	246 (60)	242 (59)	488 (59)
Pazopanib	119 (29)	131 (32)	250 (30)
Axitinib	51 (12)	50 (12)	101 (12)
Patients with quantifiable PD-L1 expression — no. (%)	370 (90)	386 (94)	756 (92)
PD-L1 expression level¶			
≥1%	94 (25)	87 (23)	181 (24)
<1%	276 (75)	299 (77)	575 (76)
≥5%	44 (12)	41 (11)	85 (11)
<5%	326 (88)	345 (89)	671 (89)
Patients without quantifiable PD-L1 expression — no. (%)	40 (10)	25 (6)	65 (8)
MSKCC=Memorial Sloan Kettering Cancer Center;			

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e) Limitations/Sources of Bias

The following should be considered as possible sources of bias in the CheckMate 025 trial:

- The trial used an open-label design, which meant that both the patients and the investigators were aware of the treatment allocation. The rationale for an open-label methodology was based on multiple factors, including different routes of administration (intravenous for nivolumab versus oral for everolimus), different treatment schedules (every two weeks for nivolumab versus daily for everolimus), different dose modification rules, different safety profiles and different management of AEs between the two study groups.[34] Although the primary endpoint of the study, OS (death), was an objective outcome, an open-label design could have introduced some levels of bias to the investigator's assessment of PFS and ORR (tumor response), patient-reported outcomes, as well as assessment and reporting of drug-related AEs.
- A small proportion of the patients who were enrolled and randomized did not receive the study treatments (approximately 1% in the nivolumab and 3% in the everolimus group). These patients were included in the intention-to-treat analysis of efficacy outcomes as randomly assigned, but were excluded from the safety analysis.
- The current review did not identify any randomized controlled trials of nivolumab versus axitinib, when used in second-line therapy, for advanced or metastatic RCC.
- Based on the available data, the interpretation of patient-reported outcomes results is limited by the manner in which data is compiled and presented. In CheckMate025, median changes from the baseline in FKSI-DRS were provided for the study treatment groups at each assessment time point, and between-group differences in median the median change values were compared statistically (using Wilcoxon-Mann-Whitney test). One potential issue with this type of comparisons is that they do not provide insight into if the changes from the baseline FSKI-DRS score in each group is important enough to guide clinical decision-making. The minimally important difference (MID) is defined as the minimal numeric change in a score that results in a meaningful difference to patients and clinicians,[37] and a MID range estimate for the FSKI-10 is suggested to be 2-4 score points.[37] In determining differences in MIDs, it is important to calculate the average mean estimates of MIDs and/or the proportion of the cases that can be categorized as 'changed' based on the suggested MID range (2-4 scores for FSKI-DRS). However, data from the identified publications does not allow us to make a judgement about MIDs.

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6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Survival (OS) *(primary outcome)*

OS was defined as the time from the date of randomization to the date of death. Study participants who did not die during the study period were censored at the end of the study or at last known alive date.[34]

In an intent-to-treat interim data analysis, after the last recruited patient had completed a minimum follow up period of 14 months, nivolumab resulted in a statistically significant improvement in median OS at 25.0 months (95% confidence interval [CI] 21.8 to not estimable), when compared with 19.6 months (95% CI 17.6 to 23.1) in the everolimus group. Overall, 183 of 410 patients assigned to nivolumab group and 215 of 411 patients assigned to everolimus died before the analysis took place. The hazard ratio (HR) of death was 0.73 (98.5% CI 0.57 to 0.93; p=0.002), indicating that nivolumab monotherapy can reduce the risk of death in previously treated advanced or metastatic RCC patients by 27%, when compared with everolimus.[1]

Subgroup analyses of OS

Results of the preplanned subgroup analyses based on according to MSKCC prognostic factor, number of prior antiangiogenic regimens, region, are demonstrated in Table 6.4. As shown, nivolumab was associated with higher OS benefit in patients with poor-risk disease (HR=0.47; 95% CI 0.30 to 0.73), those who received one prior antiangiogenic treatment (HR=0.71; 95% CI 0.56 to 0.90) and those who were recruited from US and Canada (HR=0.66; 95% CI 0.48 to 0.91). Within other subgroups, OS benefit with nivolumab was also higher as demonstrated in male patients (HR=0.73; 95% CI 0.58 to 0.92) and patients who were between 65 and 75 years of age (HR=0.64; 95% CI 0.45 to 0.91).

Additional subgroup analyses of OS, after a median follow up of 17-18 months, were presented at the 2016 ASCO Genitourinary Cancers Symposium.[9] showed consistent OS benefit associated with nivolumab across the subgroups of number and sites of metastasis, previous treatments, and Karnofsky performance status.[9] details of these subgroup analyses are shown in Table 6.4.

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Table 6.4 Subgroup analyses of overall survival in CheckMate 025[9]					
Subgroup	Nivolumab		Everolimus		HR (95% CI)
	Events/ Patients	Median OS months (95% CI)	Events/ Patients	Median OS months (95% CI)	
*MSKCC prognostic score[8]					
Favorable	38/137	NE	50/145	29.0 (26.9-NE)	0.89 (0.59 -1.32)
Intermediate	95/193	21.8 (95% CI 18.3-NE)	104/192	18.4 (95% CI 16.1-23.1)	0.76 (0.58 -0.99)
Poor	50/79	15.3 (95% CI 9.6-22.4)	61/74	7.9 (95% CI 5.4-9.7)	0.47 (0.30 -0.73)
*Region					
US/ Canada	66/174	NR	87/172	NR	0.66 (0.48 -0.91)
Western Europe	78/140	NR	84/141	NR	0.86 (0.63 -1.16)
Rest of the world	39/96	NR	44/98	NR	0.78 (0.51 -1.20)
Age (year)					
<65	111/257	NR	118/240	NR	0.78 (0.60 -1.01)
≥65 or <75	53/119	NR	77/131	NR	0.64 (0.45 -0.91)
≥75	19/34	NR	20/40	NR	1.23 (0.66 -2.31)
Sex					
Female	48/95	NR	56/107	NR	0.84 (0.57 -1.24)
Male	135/315	NR	159/304	NR	0.73 (0.58 -0.92)
Number of metastases[8]					
1	14/68	NR	21/71	NR	NR
≥2	168/341	NR	194/338	NR	NR
Sites of Metastases[8]					
Bone					
Yes	42/76	18.5 (10.2 - NE)	45/70	13.8 (7.0 -16.4)	0.72 (0.47 -1.09)
No	141/334		170/341		
Liver					
Yes	54/100	18.3 (13.4-26.7)	52/87	16.0 (8.4 -21.6)	0.81 (0.55 -1.18)
No	129/310		163/324		

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***Prior antiangiogenic therapy[8]**					
Type of treatment					
Sunitinib	123/257	23.6 (20.4-28.1)	138/261	19.8 (17.5-24.3)	0.81 (0.64-1.04)
Pazopanib	53/126	NE (19.7-NE)	79/136	17.6 (14.3-19.9)	0.60 (0.42-0.84)
Months on first-line treatment					
<6	61/110	18.2 (13.9-25.0)	81/130	14.0 (9.7-18.1)	0.76 (0.55- 1.06)
≥6	122/300	27.4 (23.2-NE)	134/281	22.8 (19.7-NE)	0.78 (0.61-0.99)
Number of prior treatments					
1	144/317	23.6 (20.8-NE)	162/312	19.9 (17.7-24.7)	0.79 (0.63-0.99)
2	37/90	NE (18.1-NE)	53/99	18.4 (14.0-NE)	NR
Karnofsky Performance Status					
90-100	NR	NE (26.7-NE)	NR	29.0 (23.4-NE)	NR
<90		18.1 (14.3-22.2)	NR	10.1 (7.9-12.8)	NR

CI= confidence interval; NE= not estimable; NR= not reported; OS= overall survival; US= United States
*Analysis were pre-specified

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Progression-free Survival (PFS)

PFS is defined as the time from randomization to the date of the first documented RECIST-defined disease progression or death due to any cause, whichever occurs first.[34] In CheckMate 025, the median PFS in the nivolumab group was reached in 4.6 months (95% CI 3.7 to 5.4), when compared with 4.4 months (95% CI 3.7 to 5.5) in the everolimus group (HR= 0.88; 95% CI 0.75 to 1.03; p=0.11).[1]

The results of an ad-hoc sensitivity analysis of PFS that was limited to study participants for whom disease progression or death outcomes had not occurred at the 6 months (35% and 31% patients in the nivolumab and everolimus arms, respectively), showed a median PFS of 15.6 months (95% CI 11.8 to 19.6) with nivolumab and 11.7 months (95% CI 10.9 to 14.7) with everolimus (HR= 0.64; 95% CI 0.47 to 0.88).[1]

Objective response rates (ORR)

ORR is defined as the number of subjects with a best response of complete response (CR; disappearance of all target lesions) or partial response (PR; ≥ 30% decrease in the sum of diameters of target lesions) divided by the number of randomized subjects.[34] In CheckMate 025, the nivolumab group showed a statistically higher ORR when compared to the everolimus group (25% versus 5%; odds ratio= 5.98; 95% CI 3.68 to 9.72; p<0.001). Complete responses were reported in 1% of patients in the nivolumab group (4 of 410 patients) and less than 1% of those in the everolimus group (2 of 411 patients).[11] Partial responses were reported in 24% of patients in the nivolumab group (99 of 410 patients) and 5% of those in the everolimus group (20 of 411 patients).[11]

The subgroup analyses of ORR suggested that nivolumab is associated with an ORR benefit across the subgroups of MSKCC risk, number and sites of metastases, and previous antiangiogenic treatments.[8,9] The results of these subgroup analyses are demonstrated in Figure 4.

Time to response

This endpoint was evaluated in subjects with a CR or PR.[34] The median time to response in CheckMate 025 was reported to be 3.5 months (range 1.4 to 24.8) in the nivolumab group and 3.7 months (range 1.5 to 11.2) in the everolimus group.[1] No statistical test results were provided in the relevant publications.

Duration of response

This endpoint was also evaluated in subjects with a CR or PR. Duration of objective response was defined as the time from first response (CR or PR) to the date of the first documented tumor progression, assessed by the investigator using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. In patients who neither had disease progression nor died, the duration of response was defined as the time from the first response (CR or PR) to the date of censoring.[34] In CheckMate 025 the median duration of response was 12.0 months (range 0 to 27.6) in the nivolumab group and 12.0 months (range 0 to 22.2) in the everolimus group.[1]

PD-L1 expression level

PD-L1 expression level was assessed as a predictive biomarker for OS in CheckMate 025.[34] Overall, 92% of the study participants (756 of 821 patients) had a quantifiable PD-L1 in their pre-treatment tumor samples. Of these 756 patients, 181 (24%) had a 1% or greater PD-L1 expression and 575 (76%) had less than 1% PD-L1 expression. As it is shown in Table 6.5, among patients with a PD-L1 expression level of 1% or greater, the median OS reached 21.8 months (95% CI 16.5 to 28.1) in the nivolumab group and 18.8 month (95% CI 11.9 to 19.9) in the everolimus group (HR= 0.79; 95% CI 0.53 to 1.17). Among patients with PD-L1 expression level of less than 1%, the median OS reached 27.4 months (95% CI 21.4 to not estimable) in the nivolumab group and 21.2 month (95% CI 17.7 to 26.2) in the everolimus group (HR= 0.77; 95% CI 0.60 to 0.97).[1]

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Table 6.5 PD-L1 expression and its association within CheckMate 025 trial[1,9]					
Subgroup	Nivolumab		Everolimus		HR (95% CI)
	Events/ Patients	Median OS months (95% CI)	Events/ Patients	Median OS months (95% CI)	
≥1%	48/94	21.8 (16.5-21.8)	51/87	18.8 (11.9-19.9)	0.79 (0.53-1.17)
<1%	118/276	27.4 (21.4-NE)	150/299	21.2 (17.7-26.2)	0.77 (0.60-0.97)
CI= confidence interval; OS= overall survival					

Patient-reported outcomes

In CheckMate 025, patient-reported outcomes assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-DRS) scale, which consists of nine symptom-specific-question self-reported questions, with a summary score that can range from 0 (the worst health status) to 36 (the best health status). The FSKI-DRS completion rate was defined as the proportion of valid questionnaires (with a minimum of 50% (5/9) of the questionnaire items completed) out of the number of patients who were still on treatment or in follow-up at each assessment point.[11] At one year, the questionnaire completion rate was 80% in the nivolumab group and 81% in the everolimus group. The median changes from the baseline FSKI-DRS score (31.0 in both study groups) was statistically better in the nivolumab group, in a consistent manner, at each assessment after baseline for patients in the nivolumab group, when compared with the everolimus arm ($p<0.05$).[1,11]

Harms Outcomes

In CheckMate 025, patients who received one or more doses of the study treatments were included in the analysis of safety outcomes. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events.[1] At the data cut-off time, treatment-related AEs of any grade were reported in 319 (79%) of 406 patients who received nivolumab and 349 (88%) of 397 patients who were treated with everolimus. Grade 3 or 4 (serious) treatment-related AEs were reported in 76 (19%) nivolumab-treated and 145 (37%) of everolimus-treated patients. Common AEs (reported in ≥ 10% of patients) in each group are shown in Table 6.6. As shown, the most common treatment-related AEs among nivolumab-treated patients were fatigue (33%), nausea (14%), and pruritus (14%); while among everolimus-treated patients, the most common AEs included fatigue (34%), stomatitis (29%) and anemia (24%). The most common grade 3 or 4 AE for patients receiving nivolumab was fatigue, which occurred in 2%, and for those receiving everolimus was anemia, which occurred in 8%.

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Table 6.6 Treatment-related adverse events reported in CheckMate 025[1]				
Adverse events	Nivolumab (n=406)		Everolimus (n=397)	
	Any grade N(%)	Grade3/4 N(%)	Any grade N(%)	Grade3/4 N(%)
All events	319 (79)	76 (19)	349 (88)	145 (37)
Most common AEs				
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0 (0)	39 (10)	0 (0)
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0 (0)	77 (19)	0 (0)
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0 (0)	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation-	11 (3)	0 (0)	75 (19)	12 (3)
Dysgeusia	11 (3)	0 (0)	51 (13)	0 (0)
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0 (0)	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0 (0)	64 (16)	20 (5)
Epistaxis	3 (1)	0 (0)	41 (10)	0 (0)

6.4 Ongoing Trials

No ongoing trials meeting the review's inclusion criteria were found.

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7 SUPPLEMENTAL QUESTIONS

No Supplemental questions were addressed in this review.

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8 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 (Opdivo) for renal cell carcinoma. 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 pCODR 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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 medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR 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.

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APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2016, **Embase** 1974 to 2016 March 03, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches
1	(Opdivo* or nivolumab* or 946414-94-4 or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ot,ab,rn,hw,nm,kf.
2	Kidney Neoplasms/
3	Carcinoma, Renal Cell/
4	exp Kidney/ and Neoplasms/
5	(kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kf.
6	(cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan*).ti,ab,kf.
7	5 and 6
8	(hypernephroma* or nephroma* or reninoma*).ti,ab,kf.
9	(RCC or mRCC).ti,ab,kf.
10	2 or 3 or 4 or 7 or 8 or 9
11	1 and 10
12	11 use pmez,cctr
13	*nivolumab/
14	(Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,kw.
15	13 or 14
16	kidney tumor/
17	kidney cancer/
18	kidney carcinoma/

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19	exp kidney/ and neoplasm/
20	(kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kw.
21	(cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan*).ti,ab,kw.
22	20 and 21
23	(hypernephroma* or nephroma* or reninoma*).ti,ab,kw.
24	(RCC or mRCC).ti,ab,kw.
25	16 or 17 or 18 or 19 or 22 or 23 or 24
26	15 and 25
27	26 use oemezd
28	12 or 27
29	limit 28 to english language

2. Literature search via PubMed

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

Search	Add to builder	Query
#6	Add	Search **(#5 AND publisher[sb])**
#5	Add	Search **(#1 AND (#2 OR #3 OR #4))**
#4	Add	Search **Hypernephroma*[tiab] OR nephroma*[tiab] OR reninoma*[tiab] OR RCC[tiab] OR mRCC[tiab]**
#3	Add	Search **(kidney*[tiab] OR renal[tiab] OR hypernephroid[tiab] OR collecting duct*[tiab] OR Grawitz[tiab] OR nephroid[tiab]) AND (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])**
#2	Add	Search **Kidney Neoplasms[mh:noexp] OR Carcinoma, Renal Cell[mh] OR (Kidney[mh] AND Neoplasms[mh:noexp])**
#1	Add	Search **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 946414-94-4[rn] OR 31YO63LBSN[rn]**

3. Cochrane Central Register of Controlled Trials (Central)

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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 terms: Opdivo OR nivolumab | kidney OR kidneys OR renal

Select international agencies including:

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

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

Search terms: Opdivo OR nivolumab

Conference abstracts:

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

European Society for Medical Oncology
http://www.esmo.org/

Search terms: Opdivo OR nivolumab | kidney OR kidneys OR renal
last 5 years

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