pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Renal Cell Carcinoma

April 2, 2020

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List of Abbreviations

AE(s)	Adverse Events
BICR	Blinded independent central review
CI	Confidence interval
CGP	Clinical Guidance Panel
CR	Complete Response
DOR	Duration of Response
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICR	Indpeedent Central Review
NSCLC	non small cell lung cancer
ORR	Overall response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression free survival
PR	Partial Response
RCC	Renal Cell Carcinoma

1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature regarding pembrolizumab (Keytruda) in combination with axitinib for renal cell carcinoma (RCC) conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pembrolizumab for RCC a summary of submitted Provincial Advisory Group Input on pembrolizumab for RCC and a summary of submitted Registered Clinician Input on pembrolizumab for RCC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of pembrolizumab (Keytruda) in combination with axitinib for the treatment of patients with advanced renal cell carcinoma (RCC), as first-line treatment.

Pembrolizumab is a selective humanized monoclonal antibody designed to block the interaction between programmed cell death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2. Pembrolizumab. The Health Canada approved indication is for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) in combination with axitinib, in adults with no prior systemic therapy for metastatic RCC[1]. The reimbursement request is for the treatment of patients with advanced renal cell carcinoma (RCC) in combination with axitinib, as first-line treatment.

According to the Health Canada Product Monograph, the recommended dose of pembrolizumab is 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression[1].

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One open-label, multinational, phase III randomized controlled trial, KEYNOTE-426 met the inclusion criteria for the systematic review. This trial was funded by Merck Sharp & Dohme. Axitinib and sunitinib were provided by Pfizer. The aim of this trial was to examine the efficacy and safety of pembrolizumab plus axitinib compared to sunitinib in patients with advanced RCC.[2] The co-primary outcomes of the trial were progression free survival and overall survival according to blinded, independent central review (BICR). The key secondary outcome was objective response rate according to BICR. Other outcomes assessed were patient reported outcomes (PROs) and safety. Crossover was not permitted

in the KEYNOTE-426 trial. Patients received subsequent therapies based on local practice.[3]

The KEYNOTE-426 trial enrolled patients across 16 countries from 124 sites.[4] The country that enrolled the most patients was the United States (n=164) followed by Japan (n=94). There were 43 patients from Canada. [5] During a maximum screening period of 28 days, patients deemed eligible were stratified according to the following factors: International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group (favorable, intermediate, or poor risk) and geographic region (North America, Western Europe, or rest of the world . Randomization was performed using an interactive voice response system / integrated web response system (IVRS/IWRS) in a 1:1 ratio to receive either pembrolizumab plus axitinib or sunitinib.[2] Pembrolizumab was intravenously administered as 200 mg every 3 weeks in combination with axitinib which was orally administered 5 mg twice daily.[2] Sunitinib was orally administered 50 mg once daily for the first 4 weeks of a 6 week cycle.[2] Key eligibility criteria included a histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features locally advanced/metastatic disease, measurable disease according to RECIST v1.1, no prior systemic therapy received for advanced RCC, KPS ≥ 70%, bone metastases treatment should have been initiated 2 weeks prior to randomization and patients should have functioning organs. [4]

According to the study authors, baseline patient characteristics were well balanced in both groups. The median age was 62 years (range: 30-89) and 61 years (range: 26-90) in the pembrolizumab plus axitinib and sunitinib group, respectively. The most common site of metastases was the lung among 312 patients (72.2%) and 309 patients (72.0%) in the pembrolizumab plus axitinib and sunitinib group respectively.[2]

Based on the trial publication, the first interim analysis occurred at the data cut off August 24, 2018. The median duration of follow up was 13.2 months (range: 0.1-21.5 months) in the pembrolizumab and axitinib group and 12.1 months (range: 0.4-22.0 months) in the sunitinib group.[4] The sponsor noted that more recent OS data was required by the EMA for the proper assessment of the benefit/risk in all relevant subgroups. Therefore, an unplanned analysis was conducted with a data cut off of January 2, 2019.[6] The median duration of follow-up at this data cut in the ITT population was 17.4 months (range: 0.1-25.6) in pembrolizumab and axitinib arm, and 15.7 months (range: 0.4-26.3) in the sunitinib arm. [4] The number of patients in the ITT population was 861 (432 patients in the pembrolizumab and axitinib group vs 429 patients in the sunitinib group). According to the sponsor, the protocol specified second interim analyses (IA2) as post marketing commitment (PMC) will be available in August 2020 and the protocol specified final analyses (FA) as PMC will be available in September 2021.[3]

Limitations

Although KEYNOTE-426 is a randomized trial, due to the open-label study design, the Sponsor, investigator, and participant were aware of the treatment administered. It is possible the trial may be at risk for biases related to blinding that can affect the internal validity. These can include bias in terms of patient selection for eligibility or performance bias because of knowledge of assigned treatment.

The secondary endpoint of duration of response was not powered to detect statistical significance. Therefore, these results should be interpreted with caution.

There was no formal hypothesis testing and no multiplicity adjustment made for PROs.[4] The Sponsor noted that patients in the sunitinib group completed the PROs following a 2-week 'off period'. Thus, the PROs assessed in the sunitinib group may not be reflected accurately as treatment with sunitinib was administered over a 6 week treatment cycle and toxicity may have been lowest at the 2 week off period in comparison to the pembrolizumab and axitinib group. Thus, there is potential bias in the PROs obtained in the sunitinib group.

The median OS was not reached in the first interim analysis and updated data cut off January 2, 2019. There is a short duration of follow-up in the trial. Long-term OS and PFS data are required to ensure the results observed in this study are consistent or maintained over a longer period of time. Furthermore, long-term safety data will help to capture delayed hepatic adverse events that may occur among patients receiving pembrolizumab treatment over time. The trial publication noted that the protocol-specified criteria for declaring a significant benefit was met for pembrolizumab and axitinib versus sunitinib for PFS and OS as reported in the first interim analysis. Therefore, no further alpha-controlled efficacy testing will be performed.[2] However, as per the trial publication, patients will continue to be followed for assessment of efficacy and safety.[4]

Outcomes

The efficacy outcomes in KEYNOTE-426 are summarized in Table 1.
All data presented are based on the first interim analysis (data cut off August 24, 2018) unless otherwise specified.

Table 1 Highlights key efficacy outcomes

	KEYNOTE-426 ITT population			
	Pembrolizumab and Axitinib (n=432)	Sunitinib (n=429)	Pembrolizumab and Axitinib(n=432)	Sunitinib (n=429)
Data cut off	August 24, 2018		January 2, 2019[4]	
Median follow-up months	13.2 months (range: 0.1-21.5 months)[4]	12.1 months (range: 0.4 - 22.0 months) [4]	17.4 months (range: 0.1-25.6 months)	15.7 months (range: 0.4-26.3 months)
Co-Primary Outcomes				
PFS				
Events n (%)	183 (42.4)[2]	212 (49.7)[2]	207 (47.9)	232 (54.1)
Median PFS (95% CI)	15.1 months (12.6-17.7)[2]	11.1 months (8.7-12.5)[2]	17.1 months (13.6-18.9)	11.1 months (8.7-12.5)
PFS rate at 12 months % (95% CI)	59.6% (54.3-64.5)[4]	46.1% (40.5-51.5)[4]	60.1% (55.1-64.7)	47.7% (42.5-52.7)
PFS rate at 18 months % (95% CI)	41.1% (95% CI 33.5-48.5)[4]	32.8% (25.4-40.4) [4]	Not reported	Not reported
HR (95% CI)	0.69 (0.56-0.84) P<0.001[2]		0.69 (0.57-0.83) P=0.00005	
OS				
Events n (%)	59 (13.7) [2]	97 (22.6) [2]	84 (19.4)	122 (28.4)
Median OS months (95% CI)	Not reached[2]	Not reached [2]	Not reached	Not reached
HR (95% CI) p-value	0.53(0.38-0.74), P<0.0001[2]		0.59 (0.45-0.78, P=0.0001	
OS rate at 12 months	89.9% (86.4-92.4) [2]	78.3% (73.8-82.1) [2]	89.5% (86.2-92.1)	78.8% (74.7-82.4
OS rate at 18 months	82.3% (77.2-86.3) [2]	72.1% (66.3-77.0) [2]	81.0% (76.7-84.6)	70.7% (65.8-75.1)
Key Secondary Outcomes				

	KEYNOTE-426 ITT population			
ORR % (95% CI)	**59.3% (54.5-63.9) [2]**	**35.7% (31.1-40.4) [2]**	**60.0% (55.2-64.6)**	**38.5% (33.8 - 43.2)**
DOR				
Median DOR (range)	**Not reached (1.4+ - 18.2+ months) [2]**	**15.2 months (range:, 1.1+ - 15.4+)[2]**	**Not reported**	
Time to Response Median (Range)	**2.8 (1.5-16.6)[2]**	**2.9 (2.1-15.1) [2]**	**Not reported**	
Harms Outcome				
Grade ≥3 %	**75.8[2]**	**70.6[2]**	**Not reported**	
AE (any grade) n (%)	**422 (98.4)[2]**	**423(99.5) [2]**	**Not reported**	
AE Grade 3 or higher n (%)				
Hypertension	**91(21.2)[2]**	**78 (18.4) [2]**		
Diarrhea	**31(7.2) [2]**	**19 (4.5) [2]**	**Not reported**	
PFS= progression free survival, OS= overall survival, DOR= duration of response, ORR= objective response rate, AE = adverse event, CI = confidence interval, HR = hazard ratio,				

Co-Primary Outcomes

Progression Free Survival-BICR assessed

The number of events in the pembrolizumab plus axitinib group was 183 (42.4%) compared to 213 events (49.7%) in the sunitinib group. Progression was documented in 162 patients (37.5%) in the pembrolizumab and axitinib group compared to 184 patients (42.9%) in the sunitinib group.[4] The median progression-free survival improved by 4 months (15.1 months, 95% CI: 12.6-17.7) in the pembrolizumab plus axitinib group compared to the sunitinib group (11.1 months,95% CI: 8.7-12.5). There was a statistically significant improvement for disease progression or death in favour of the pembrolizumab and axitinib group compared to sunitinib in the ITT population (HR=0.69,95% CI: 0.57 to 0.84, p<0.001).[2] The first interim analysis for PFS was statistically significant and crossed the prespecified boundary of 0.0013. [4] The magnitude of the effect size and 95% CI was consistent at the updated data cut off of January 2, 2019 in the ITT population which demonstrated an improvement in PFS in favour of the pembrolizumab and axitinib group compared to sunitinib.

The exploratory subgroup analyses of PFS suggests the subgroup analyses of PFS are generally consistent with the overall trial results.

Overall Survival-BICR assessed

The number of events in the pembrolizumab and axitinib group was 59 (13.7%) compared to 97 events in the sunitinib group (22.6%). [4] The median OS was not reached in either group. There was a statistically significant improvement for OS in favour of the pembrolizumab plus axitinib group compared to the sunitinib group in the ITT population (HR=0.53,95% CI: 0.38- 0.74; P<0.0001).[2] The first interim analysis for OS was statistically significant and crossed the prespecified boundary of 0.0001.. [4] The exploratory subgroup analyses of OS suggests these results are consistent with the overall trial results. At an unplanned data cut-off of January 2, 2019, the HR and 95% CI had a smaller effect size in OS in the ITT population HR= 0.59 (95% CI: 0.45-0.78, P=0.0001). [4]

Secondary Outcomes

Objective Response Rate-BICR assessment

Since the co-primary endpoints of PFS and OS assessed by BICR met the thresholds in the first interim analysis, the key secondary outcome of objective response rate was assessed.

The objective response rate was higher in the pembrolizumab plus axitinib group of 59.3% (95% CI: 54.5-63.9) compared to 35.7% (95% CI: 31.1-40.4) in the sunitinib group. [4]A complete response was reported in 25 patients (5.8%) in the pembrolizumab plus axitinib group and 8 patients (1.9%) in the sunitinib group. Partial response was observed in 231 patients (53.5%) in the pembrolizumab plus axitinib group versus 145 patients (33.8%) in the sunitinib group.[2]

At the updated data cut off of January 2, 2019 in the ITT population, the objective response rate in the pembrolizumab plus axitinib group was consistent with the August 24, 2018 data cut off and slightly higher in the sunitinib group. The subgroup analyses conducted at the data cut off January 2, 2019 demonstrated consistent results with the August 24, 2018 data cut off.

Duration of Response-BICR assessed

The median duration of response was not reached in the pembrolizumab plus axitinib group (range: 1.4+ to 18.2+ months), and the median duration of response was 15.2 months (range: 1.1+ to 15.4+) in the sunitinib group.[2] The median time to response was 2.8 months (range: 1.5-16.6) in the pembrolizumab and axitinib group compared to 2.9 months (range: 2.1-15.1) in the sunitinib group. [4]Approximately 70.6% of patients reported an ongoing response at 1 year in the pembrolizumab plus axitinib group and 61.6% in the sunitinib group. [2]

Patient Reported Outcomes

Pembrolizumab-axitinib did not result in meaningful changes in the FKSI-DRS compared with sunitinib.[7]The median time to true deterioration was not reached in either treatment group.[4] There was no statistically significant difference in the time to true deterioration assessed by the FKSI-DRS (i.e., time to first onset of 3 or more decrease from baseline with confirmation under right-censoring rule) between the pembrolizumab and axitinib group and sunitinib group (HR 1.44, 95% CI: 1.14-1.82; nominal p=0.999).[4]

For the EORTC QLQ-C30, the change from baseline to week 30 based on the least square mean calculated between the pembrolizumab plus axitinib group and the sunitinib group was not statistically significant -1.70 (95% CI: -4.34-0.94), p=0.207.[7]

There were no clinically meaningful differences from baseline to week 30 in the EORTC QLQ-C30 global health status/QoL score in both study groups. [4]

From baseline to week 30, for the EORTC QLQ-C30 functional scales (i.e., physical functioning and role functioning) and the symptom scales (i.e., nausea and vomiting), there was no statistically significant difference between the pembrolizumab plus axitinib group compared to sunitinib. However, for the symptom scale of diarrhea, from baseline to week 30, worsening symptoms of diarrhea was observed in the pembrolizumab plus axitinib group compared to sunitinib.[7,4] The sponsor conducted an exploratory adjustment for treatment exposure, which resulted in a similar event rate of diarrhea between the pembrolizumab plus axitinib group and sunitinib group.[6]

Safety

In the as-treated study population, among the 429 patients that received at least one of pembrolizumab plus axitinib, 98.4% experienced an adverse event of any cause compared to 99.5% of the 425 patients who received sunitinib experienced adverse events of any cause.[2] Grade 3 or higher AEs were slightly higher in 75.8% of patients in the pembrolizumab plus axitinib group compared to 70.6% of patients in the sunitinib group. Hypertension was the most common Grade 3 or higher AE that occurred in the pembrolizumab plus axitinib group (21.2%) and sunitinib (18.4%) followed by diarrhea in the pembrolizumab plus axitinib group (7.2%) versus sunitinib group (4.5%).

In the pembrolizumab and axitinib group, discontinuation of either drug due to adverse events of any cause occurred in 30.5% of patients, discontinuation of both pembrolizumab and axitinib in 10.7% of patients, interruption of either drug in 69.9% of patients, and dose reduction of axitinib in 20.3%. Four patients (0.9%) in the pembrolizumab and axitinib group died from adverse events attributed to study treatment by the investigator (i.e., one patient each of myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis). There were seven patients (1.6%) in the sunitinib group whom died from adverse events attributed to study treatment by the investigator (i.e., one patient each of acute myocardial infarction, cardiac arrest, gastrointestinal hemorrhage, hemorrhage intracranial, hepatitis fulminant, malignant neoplasm progression, and pneumonia).[2] No deaths related to study drug were reported.

At the updated data cut off of January 2, 2019, 65 patients (15.2%) in the pembrolizumab and axitinib arm and 61 patients (14.4%) in the sunitinib arm had discontinued study treatment(s) due to adverse events.[4]

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

One patient advocacy group, Kidney Cancer Canada (KCC), provided input on the pembrolizumab in combination with axitinib for RCC review. An online survey of patients and caregivers with experience with pembrolizumab in combination with axitinib was conducted between August 9, 2019 to August 15, 2019. One patient and one caregiver responded to the online survey. KCC also contacted other kidney cancer patient organizations in the UK and U.S. to find patients with experience with this treatment combination. A total of seven patients, with experience with the pembrolizumab and axitinib combination participated in the Kidney Cancer UK survey.

From a patient's perspective, patients considered pembrolizumab+axitinib to be a very effective drug combination with minimal and manageable side effects. Many patients reported a better quality of life with minimal disruptions to their daily routine. Additionally, many expressed optimism for future therapies in providing more precise targeted treatment and better ability to tailor the treatments plans to suit the individual needs of each patient. Overall, patients value increased awareness and earlier detection of disease, delay in disease progression and increased support in helping manage the disease.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Place in therapy and sequencing with currently available treatments

Economic factors:

- Clarity on dosing schedule and treatment duration

Please see below for more details.

Registered Clinician Input

One joint input submission on behalf of three oncologists from Cancer Care Ontario and one joint submission on behalf of two oncologists from Kidney Cancer Research Network of Canada (KCRNC) were submitted for the review of pembrolizumab+axitinib for patients with advanced renal cell carcinoma (RCC). Based on the results of the KEYNOTE-426 trial, all clinicians agreed that pembrolizumab+axitinib would be a beneficial first-line combination therapy for previously untreated patients with advanced RCC, inclusive of all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)) risk groups. All clinicians acknowledged that robust data on optimal sequencing of therapies is not currently available. A variety of possible sequencing options were presented by each clinician input based on current data and clinician practice. The clinicians noted that compared to sunitinib, pembrolizumab+axitinib showed a significantly longer overall survival (OS) and progression-free survival (PFS) as well as a higher objective response rate (ORR), with similar tolerance profiles

Summary of Supplemental Questions

The following Supplemental Questions were identified while developing the review protocol as relevant to the pCODR review of pembrolizumab plus axitinib:

- Summary of sponsor-submitted network meta-analysis (NMA) comparing pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma

  The Sponsor conducted a systematic literature review to identify RCTs and systematic reviews that evaluated objective response rate (ORR), progression free survival (PFS), overall survival (OS), and safety for patients with mRCC.

  In the constant HR base case analysis of PFS, pembrolizumab + axitinib resulted in a statistically meaningful increase in the duration of PFS compared to all competing interventions except avelumab + axitinib and nivolumab + ipilimumab. In the constant HR base case analysis of OS, treatment with pembrolizumab + axitinib resulted in a statistically meaningful increase in the duration of OS compared to all competing interventions except avelumab + axitinib and nivolumab + ipilimumab.

  Among the intermediate and poor risk subgroup, the results of the PFS and OS constant HR analyses both showed that pembrolizumab + axitinib was statistically superior to sunitinib, but not cabozantinib or nivolumab + ipilimumab.

  In appraising the NMA, the pCODR review team identified the following limitations: the lack of clarity on the inclusion and exclusion criteria, sources of clinical heterogeneity

and lack of clarity of baseline characteristics of patients included in the trials, missing data. Due to the limitations identified, results of the NMA should be interpreted with caution. The relative efficacy of pembrolizumab + axitinib versus other competition interventions remains uncertain for the first line treatment of metastatic renal cell carcinoma.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

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

Table 2: Assessment of generalizability of evidence for Pembrolizumab for advanced renal cell carcinoma

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Karnofsky Performance Status (KPS)	Inclusion criteria specified patients were required to have a KPS ≥70.	Do the results apply to patients with KPS <70?	The CGP agree that it is reasonable to generalize the trial results to patients with KPS<70 at the discretion of the treating oncologist. In addition, the CGP noted that patients with ECOG performance status of 0-2 would be eligible for the treatment combination.
	Metastatic Sites	Patients with CNS metastases were excluded from the trial	Are the KEYNOTE-426 trial results generalizable to patients with non-active brain metastases?	The CGP noted that patients with non-active brain metastases should be eligible to receive the combination of pembrolizumab plus axitinib
	Histologic type of disease	The KEYNOTE-426 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)?	The CGP noted that in general patients with non-clear cell RCC are managed the same way as patients with clear cell RCC. The CGP therefore agree that patients with non-clear cell histology should be eligible for treatment with pembrolizumab plus axitinib in this setting[8].

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Treatment duration.	Pembrolizumab was administered for a maximum of 35 cycles.	As patients could receive a total of 35 cycles or for 24 months. If as treatment interruptions due to toxicity occurs before the 35 cycles are administered and patients have reached the 24 months years, could treatment continue beyond two years.	Based on clinical opinion, the CGP agreed that treatment with pembrolizumab and axitinib should continue up to a maximum of 35 cycles and the treatment could continue beyond the two years if the maximum number of cycles has not yet been reached.
	Dosing	In the KEYNOTE-426 trial, Pembrolizumab was administered intravenously at a dose of 200 mg once every 3 weeks	Could an alternate dosing schedule be used (i.e., weight based of 2mg/kg up to 200mg, 400mg or 4mg/kg up to a flat dose cap of 400mg every 6 weeks).	The CGP agreed that an alternative weight-based dosing schedule would be reasonable to use.
Comparator	pembrolizumab plus axitinib compared to the standard of care at the time, sunitinib.	KEYNOTE-426 trial compares pembrolizumab plus axitinib to sunitinib. Pazopanib for the first line treatment of RCC is a currently funded option and nivolumab +ipilimumab for intermediate/poor risk patients with previously untreated, advanced or metastatic renal cell carcinoma has been recommended for funding.	Can the trial results be generalized to patients receiving other first-line therapies (e.g, Nivolumab and ipilimumab, pazopanib)	The CGP noted that sunitinib was a valid comparator when the trial was initiated. The CGP also noted that pazopanib and nivolumab plus ipilimumab are both recommended by pCODR for the treatment of RCC. The CGP commented that a head to head trial comparing pembrolizumab in combination with axitinib to these therapies would be unlikely.

1.2.4 Interpretation

Burden of Illness and Need

Until recently the standard first line treatment for mRCC consisted of either sunitinib or pazopanib. Although well tolerated and effective, these treatments are not curative and most patients will progress, underscoring the urgent need for novel treatment approaches. The checkpoint inhibitors, that target PD-1, such as nivolumab, have shown encouraging activity and are currently approved in the second line mRCC setting[9]. Interest has now shifted to moving these

agents earlier and exploring combination approaches which have already shown early success. In the first line setting, the combination of two checkpoint inhibitors, ipilimumab and nivolumab was shown to be superior to sunitinib in intermediate and poor risk patients and is now a Health Canada approved regimen in intermediate and poor risk patients[2]. Another strategy involves combining a checkpoint inhibitor with an angiogenesis inhibitor.

At this time, no predictive biomarkers exist which would allow the rationale selection of single agent or combination therapy for individual patients. Long-term survival and cure are still rare for patients with mRCC. Thus, there remains an unmet need for novel therapies which are associated with increased efficacy and in particular increased overall survival.

Effectiveness:

KEYNOTE-426 was an open-label randomized phase III trial comparing pembrolizumab plus axitinib versus sunitinib in treatment naïve patients with mRCC. At the time the study was conducted, sunitinib was an appropriate comparator.[2] The results below are reflective of the planned first interim analysis.[2]

Main inclusion criteria were comparable to the inclusion criteria of other randomized trials in this setting and included patients with a Karnofsky performance status of 70 or better, clear cell or clear cell component histology, and absence of active brain metastases. Among 1062 patients, the median age was 62, most were male, and just over half in each arm were intermediate risk by IMDC criteria.

At the first interim analysis, the objective response rate was 59.3% (95% CI: 54.5-63.9) in the pembrolizumab plus axitinib group and 35.7% (95% CI: 31.1-40.4) in the sunitinib group (P<0.001); 5.8% of patients in the pembrolizumab plus axitinib group and 1.9% in the sunitinib group had a complete response. The median duration of response was not reached in the pembrolizumab plus axitinib group (range: 1.4+ to 18.2+ months), and the median duration of response was 15.2 months (range: 1.1+ to 15.4+) in the sunitinib group. The estimated percentage of patients with an ongoing response at 1 year was 70.6% in the pembrolizumab plus axitinib group and 61.6% in the sunitinib group. Overall pembrolizumab plus axitinib shows one of the highest objective response rates reported in the first line setting, even compared to the combination of ipilumumab and nivolumab which was reported to be 42% in the Phase 3 trial. Pembrolizumab plus axitinib has not been compared head to head against ipilimumab plus nivolumab but may be the favored option in situations where a rapid clinical response is desired[10].

In terms of overall survival, the estimated percentage of patients who were alive at 12 months was 89.9% (95% CI: 86.4-92.4) in the pembrolizumab plus axitinib group compared to 78.3% (95% CI: 73.8-82.1) in the sunitinib group. The corresponding estimates for 18 month survival were 82.3% (95% CI: 77.2-86.3) and 72.1% (95% CI: 66.3-77.0). The median survival was not reached in either group. The risk of death was 47% lower in the pembrolizumab plus axitinib group than in the sunitinib group (HR 0.53; 95% CI: 0.38-0.74; P<0.0001). The median PFS was 15.1 months (95% CI: 12.6-17.7) in the pembrolizumab plus axitinib group and 11.1 months (95% CI: 8.7-12.5) in the sunitinib group (Figure 2A). The HR for disease progression or death was 0.69 (95% CI: 0.57-0.84; P<0.001). The benefits of pembrolizumab plus axitinib with respect to overall survival and progression-free survival were observed in all subgroups examined, including all IMDC risk and PD-L1 expression categories. This improvement in overall and progression free survival seen with pembrolizumab plus axitinib is clinically and statistically significant. Although subgroup analyses should be viewed with caution it is notable that the benefit of pembrolizumab plus axitinib was observed across all subgroups tested, including all IMDC risk groups and in patients with and without PD-L1 expression. The fact that it improves survival regardless of subgroup distinguishes

this regimen from the Ipilimumab+Nivolumab regimen which showed a benefit over sunitinib only in the poor and intermediate risk groups and provides a new option for patients in the favorable risk category[10].

The sponsor's submitted network meta analysis (NMA) suggested that the pembrolizumab and axitinib combination was favored over all the other competing interventions however there are differences in the patient and study characteristics and the presence of clinical heterogeneity limits the robustness of these results and thus they are to be interpreted with caution. In addition, results from the sponsor's network meta analysis noted the statistical significance of pembrolizumab and axitinib for duration of PFS and OS; however, due to the limitations identified earlier, the results are to be interpreted with caution.

In terms of quality of life, pembrolizumab plus axitinib did not result in meaningful changes in the FKSI-DRS compared with sunitinib and there was no clinically meaningful difference from baseline to Week 30 in the EORTC QLQ-C30 global health status/QoL score in both study groups. For the EORTC QLQ-C30 functional scales (i.e., physical functioning and role functioning) and the symptom scales (i.e., nausea and vomiting), there was no statistically significant difference between the pembrolizumab plus axitinib group compared to sunitinib. Overall it appears that there is, there was no detriment to quality of life in the pembrolizumab plus axitinib arm compared to sunitinib.

The consistent improvement in all three endpoints ORR, PFS and OS and lack of a negative impact on QOL, observed with pembrolizumab plus axitinib make it a strong choice in the first-line mRCC setting. Also important is the fact that some patients will not get to second line therapy due to disease progression, so having a regimen that combines both a checkpoint inhibitor and an angiogenesis inhibitor in front line is important.

It is also notable that the efficacy of sunitinib in this trial compares favorably with the results published in the literature making it very unlikely that the superiority of pembrolizumab plus axitinib was caused by suboptimal activity of single agent sunitinib.

The observed safety profiles of pembrolizumab plus axitinib and of sunitinib were as expected on the basis of the known profiles of these drugs, although the incidence of grade 3 or 4 elevations in liver-enzyme levels in the pembrolizumab plus axitinib group was higher than seen when each agent was used as monotherapy. There were no deaths related to hepatic adverse events in the pembrolizumab plus axitinib group. Further characterization of hepatic adverse events in this trial is ongoing and required longer term follow-up. Discontinuation of any treatment because of adverse events occurred more frequently in the pembrolizumab plus axitinib group than in the sunitinib group. The incidence and severity of adverse events of interest were as expected. The exception was a greater incidence of thyroid dysfunction but this was not unexpected. Overall the toxicity of the pembrolizumab plus axitinib regimen would be considered acceptable and manageable. Although not compared head to head, the toxicity profile of pembrolizumab plus axitinib is different than other treatments for the first line therapy for patients and this would be a consideration for treatment choice.

Generalization and applicability of these results to certain patient populations:

Non-clear cell Histology

The current study was limited to patients with ccRCC. It excluded patients with non-clear cell (ncRCC) histology. ncRCCs are rare and include a variety of histologically and genetically distinct subtypes with papillary, chromophobe, oncocytoma and collecting duct subtypes being the most common. Due to the heterogeneity and small patient numbers, conducting large clinical trials in

this setting has been challenging. There is data to support the use of both angiogenesis inhibitors and checkpoint inhibitors in this setting.[8] Today, most ncRCC patients are treated according to ccRCC guidelines despite the lack of large randomized studies. Based on this, pembrolizumab plus axitinib should be made available to patients with non-clear cell histology.

Performance Status

Patients with performance status 2 or 3 represent a particular problem since almost all randomized RCC studies to date have excluded them. However, performance status should not be a criterion to exclude patients from pembrolizumab plus axitinib. Real world data with other targeted agents such as sunitinib have shown a good benefit for TKIs even in patients with performance status 2 although these patients may have been excluded from the pivotal studies. There is no biologic reason why patients with performance status > 1 should respond differently to pembrolizumab plus axitinib. Given the toxicity of pembrolizumab plus axitinib, we would caution its use in very poor performance status, ECOG > 2 patients.

KEYNOTE-426 was a study conducted in treatment naïve mRCC patients. Patients currently receiving first line treatment, should not be switched to this regimen if it was to be approved. They should continue their first line treatment and could consider receiving checkpoint inhibitors in second line. On the KEYNOTE-426 study, over half the patients in both arms who discontinued treatment went on to receive subsequent treatments. In the pembrolizumab plus axitinib arm, 44% received an angiogenesis inhibitor-either sunitinib or cabozantinib; in patients receiving sunitinib, about a 1/3 received a second line angiogenesis inhibitor and another 1/3 received a checkpoint inhibitor. This would likely be similar to what would be seen in routine practice.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit for pembrolizumab plus axitinib in the first line mRCC setting regardless of IMDC subgroup or PD-L1 expression level compared to sunitinib. This was based on the KEYNOTE-426 randomized Phase III trial that demonstrated a clinically meaningful and statistically significant benefit in response rate, PFS and OS for pembrolizumab plus axitinib compared with sunitinib in patients with mRCC clear cell or clear cell component carcinoma. Based on previous experience with both TKIs and checkpoint inhibitors, the toxicity of pembrolizumab plus axitinib was felt to be acceptable. In light of the rarity of non-clear cell mRCC, the lack of treatment options or large randomized trials, and high unmet need, it was felt that these patients should not be excluded from pembrolizumab plus axitinib in first line.

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 and none of these options are considered curative.
- Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines. Pembrolizumab plus axitinib should therefore be made available to patients with non clear-cell histology.
- As with other targeted agents, pembrolizumab plus axitinib has an acceptable and manageable toxicity profile, which will safely allow treatment for patients with

performance status 0-2. This is consistent with current clinical practice where patients with performance status 0-2 are treated with sunitinib and have shown a good benefit even though these patients may have been excluded from the KEYNOTE-426, based on a KPS below 70.

- In clinical practice, patients with stable brain metastases are treated the same way as patients without brain metastases. Therefore, patients with stable brain metastases should not be excluded from treatment with pembrolizumab plus axitinib .
- The results of this trial are not generalizable to the second-line setting.
- Patients who are currently receiving and responding to first line treatment should not be switched to pembrolizumab plus axitinib which is for patients who are treatment naïve mRCC.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2019 an estimated 7200 Canadians will be diagnosed with kidney cancer: 1900 will die from the disease.[11] About 85% of kidney cancers are renal cell cancers (RCC) which are genetically and histologically distinct from carcinomas arising from the renal pelvis, which are known as urothelial carcinomas and managed differently. Histologically most RCCs are classified as clear cell carcinomas, with a subset of patients have non-clear cell carcinoma. At presentation, 75% of patients will have localized disease confined to the kidney, of which 50% will eventually relapse and metastasize. Another 25% will already be metastatic at presentation. Among patients with metastatic disease 75% will have intermediate or poor prognosis. The most important prognostic factor for outcome is tumor stage, and patients with metastatic disease are rarely cured, although with novel treatment approaches, outcomes are getting better.

The most commonly used classification for mRCC previously was the MSKCC criteria which included 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 in clinical trials to determine eligibility. The IMDC criteria describes a more extensive prognostic risk model and has been shown to improve in predicting prognosis and is the classification commonly used today.

2.2 Accepted Clinical Practice

Until recently, for patients with mRCC standard first line treatment consisted of either Sunitinib or Pazopanib - both small molecule tyrosine kinase inhibitors of the vascular-endothelial-growth-factor (VEGF) receptor. More recently it has been shown in patients with intermediate or poor risk disease as defined by IMDC, that the combination of the checkpoint inhibitors Ipilumumab and Nivolumab (Ipi/Nivo) was superior to Sunitinib [10]. The Ipi/Nivo regimen is Health Canada approved in the first line setting for these patients. However, not all patients will be considered to

be candidates for this regimen due to risk of toxicity, underscoring the unmet need for alternate strategies that are both well tolerated and effective.

Patients with Renal Cell Carcinoma		
Line of Therapy	Favorable Risk	Intermediate/Poor Risk
1st-Line	Sunitinib, Pazopanib	Sunitinib, Pazopanib, Nivolumab+Ipilimumab
2nd line	Axitinib, Everolimus	Axitinib, Everolimus

2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of Pembrolizumab and Axitinb for patient with the following criteria

- Metastatic or advanced inoperable renal cell carcinoma
- No prior systemic treatment for metastatic disease

Currently there are no clinically useful and reliable biomarkers for the prediction of response or benefit in this population.

2.4 Other Patient Populations in Whom the Drug May Be Used

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

3 SUMMARY OF PATIENT ADVOCACY GROUP

The following patient advocacy group(s) provided input on Pembrolizumab for renal cell carcinoma (RCC): Kidney Cancer Canada (KCC) and Kidney Cancer UK (KCUK). KCC conducted an online survey for patients and caregivers with experience with pembrolizumab+axitinib from August 9, 2018 to August 15, 2018. The survey was shared through social media and aimed to assess the impacts of this treatment combination on kidney cancer patients. Four Canadian investigators on the KEYNOTE-426 trial were requested to forward the survey link to the patients enrolled in the trial. A total of 2 respondents (one patient and one caregiver) responded to the survey. KCC acknowledged that there are very few patients with experience with this treatment combination in Canada, given that there are currently no other means in Canada of accessing pembrolizumab+axitinib outside of the KEYNOTE-426 trial. Although the KEYNOTE-426 trial has a world-wide enrolment of 861 patients with 432 patients randomized to the pembrolizumab+axitinib arm, only 104 patients are in North America across approximately 25 active sites, with only 4 of the sites being in Canada. The survey consisted of free-form commentary, scoring options and limited closed questions. A live telephone interview was conducted using an interview guide, with specific questions focused on quality of life while being treated with pembrolizumab+axitinib. A follow-up telephone interview was conducted with the caregiver to understand their experience and insights into the pembrolizumab+axitinib treatment combination.

KCUK previously conducted a survey designed by The National Institute for Health and Care Excellence (NICE), UK Department of Health on patients experiencing treatment with pembrolizumab+axitinib and provided results of that survey to KCC. This survey was administered by KCUK in May and June 2019 and consisted of a standard instrument (*Patient Carer Organisation Submission Template*) which was provided to patient groups by the National Institute of Health and Care Excellence (NICE). KCUK received responses through a mix of email and live telephone interviews. KCUK sought participation in the survey through a notice posted on the KCUK Patient Support Group (a closed Facebook Group) and also reached out directly to patients known to be on this treatment combination. A total of seven patients, with experience with the pembrolizumab+axitinib combination participated in the KCUK survey.

The patient input provided by KCC reflects the results of KCC's survey, the survey results from KCUK, and the one-on-one interview with a caregiver.

From a patient's perspective, patients considered pembrolizumab+axitinib to be a very effective drug combination with minimal and manageable side effects. Many patients reported a better quality of life with minimal disruptions to their daily routine. Additionally, many expressed optimism for future therapies in providing more precise targeted treatment and better ability to tailor the treatments plans to suit the individual needs of each patient. Overall, patients value increased awareness, earlier detection of disease, delay in disease progression and increased support in helping manage the disease.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Renal Cell Carcinoma

Metastatic renal cell carcinoma (mRCC) is a fatal disease with no known cure. For patients diagnosed with stage IV disease, the survival rate is poor with less than 10% of these patients surviving for 5 years or longer. Nonetheless, survival for patients with kidney cancer has significantly improved over the last decade with evolving treatments and improved access to those treatments. A challenge highlighted for patients with mRCC and the physicians who treat it is that complete response to treatment with a single agent is rare, with eventual resistance to existing available first-line treatment being almost certain.

In the CKUK survey, patients were asked if they believe that there is an unmet need for patients with kidney cancer. One patient specified the unmet need to be the earlier detection of kidney cancer and more research and availability of drugs. A consistent theme in the responses was the importance of having as much support as possible after diagnosis. One patient commented: *"Thanks to Kidney Cancer UK, …I would have felt very alone with this condition. Initially when I first lost my Kidney, then the outlook was a case of, the tumour has been removed with a good margin therefore, that should be the end of it! I felt very isolated, information was not easily available regarding counselling or the chance for reassurance."*

3.1.2 Patients' Experiences with Current Therapy for Renal Cell Carcinoma

For this patient input, KCC did not provide any direct insights into patients' experience with currently available treatments for mRCC. KCC advised pCODR to refer to previous KCC patient input submissions for previous pCODR reviewed drugs - axitinib (Inlyta) 2012; pazopanib (Votrient) 2013; nivolumab (Opdivo) 2016; cabozantinib (Cabometyx) 2018.

The following data were retrieved from the 2018 submission of Cabozantinib (Cabometyx) for renal cell carcinoma, submitted by Ipsen Biopharmaceuticals Canada. For this submission, KCC had provided patient input to pCODR for review, in which patient experiences regarding current treatments was provided.

Table 1 lists the treatments used by among the 105 patients who were surveyed.

Table 1. Treatments Used by Patients

Treatment	Number of patients
Sunitinib	87
Temsirolimus	4
Everolimus	20
Axitinib	19
Pazopanib	29
Sorafenib	7
Nivolumab	38
High dose interleukin 2	11

Patients were asked, "In general, how would you rate the side effects of these treatments with 1 being "completely intolerable" and 5 being "very tolerable?" The weighted average of all patients was 3.15, indicating that most patients find current drugs to be generally

tolerable, but with approximately 23% selecting either "1" or "2". It is clear that a significant number of patients find certain treatments to be intolerable and require treatment options throughout their care pathways. Results for this question are presented in the table 2.

Table 2: Patient Ratings of Current Treatment Side-Effects

1 - Completely intolerable	2	3	4	5 Very tolerable	Total	Weighted Average (WA)
3.81% (n=4)	19.05% (n=20)	44.76% (n=47)	22.86% (n=24)	9.52% (n=10)	105	3.15

Additional patient input submissions provided to pCODR were referred to (nivolumab 2016, axitinib 2012, pazopanib 2011), in which KCC reported extensively on various aspects of patient experience with current treatments. The recurring themes in these surveys included the following:

- Having a choice was considered very important when considering a new therapy, giving patients an opportunity to have an informed choice on treatment based on known side effects
- Current treatment options are not effective for everyone and can be difficult to access
- There is a high or unmet patient need in current therapy based on first-line therapy selection as many patients become refractory to first-line treatment

KCC also commented that biomarkers for RCC treatment have not yet been identified and clinicians are not always able to predict which patients will respond to which treatment. Increasing the choices of treatments for patients will eventually result in more personalized therapy, enabling patients and clinicians to tailor treatment plans to suite the individuals needs of each patient.

3.1.3 Impact of Renal Cell Carcinoma and Current Therapy on Caregivers

The one caregiver that responded to the KCC survey was the daughter of a patient with RCC. She was a statistician by profession who was working from home while caring for her mother. The caregiver stated that she accompanied her mother to all her physician visits, imaging appointments and tracked all treatments and their side effects. She mentioned that her responsibilities of looking after her mother had significantly impacted her ability to work, but that she had managed to find some flexibility in her work schedule and was able to provide the needed care for her mother during her cancer treatment. Furthermore, the caregiver reported that treatment *"went very well from the outset, with the first two sets of treatments determining that her mother was responding*". Her mother missed 3 cycles due to diarrhea and gastric issues, with the treating physician believing that the earlier bowel resection was the likely cause. It was reported that the effect of pembrolizumab+axitinib was significantly effective and that this drug combination is a "game changer" which should be made available to all patients with mRCC.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Pembrolizumab or New Therapies

KCC acknowledged that although newer therapies within the last 12 years have improved overall patient outcomes, there exists a need for therapies to do more to improve the outlook of patients

with advanced RCC. Effective therapies are needed with manageable side effects that are not resistant to antiangiogenic therapies. Additionally, effective predictive and prognostic biomarkers are needed to help detect the disease at an earlier stage and guide treatments plans for patients, thus leading to improved patient outcomes. The CKUK survey asked patients about any additional issues that they would like to be considered. Many patients mentioned the importance of increased awareness of the disease, preventative measures and early screening in order to identify treatable conditions before surgery is required. One patient further mentioned that early screening would be cost beneficial to the healthcare system as well. One patient commented: "*The treatment may not work for all patients, thus is there a way of predicting who would likely benefit, based on research, and clinical experience, thus making it's use more cost effective.*"

3.2.2 Patient Experiences to Date with Pembrolizumab+axitinib

The one patient that responded to the KCC survey was a 77-year old female who was diagnosed with RCC in 2010. This patient had qualified for the KEYNOTE-426 trial and was randomized to the pembrolizumab+axitinib arm. Overall, the patient reported that she was satisfied with her experience with pembrolizumab+axitinib and was optimistic about her prognosis. Based on personal experience, she rated pembrolizumab+axitinib as "5-extremely effective" (*1 being "not effective" and 5 being "extremely effective")* in controlling her kidney cancer. When asked to rate her quality of life while taking pembrolizumab+axitinib on a scale of 1 to 5 (1 being "low/seriously impacted", and 5 being "high/normal living"), the patient responded with a 3 ("moderately impacted"). She was further asked to explain how pembrolizumab+axitinib has changed or how it is expected to change her long-term health and wellbeing. She responded: "*We are hoping my body has learned to fight cancer using my immune system. In any case, my tumour has shrunk and will, I hope continue to stay the same.*"

When asked to report any side effects she found the most difficult to tolerate, the patient reported extreme tiredness and dietary problems.
In addition to the question above, the patient was also provided with a list of 19 known side effects and was asked to report the ones she had experienced the most. Out of the 19 side effects, the patient identified 6 that she had experienced the most. She was additionally asked to rate these side effects on a scale from 1 to 5, with 1 being "completely intolerable" and 5 being "very tolerable" and reported as follows:

- Skin problems including itching (pruritus) and rash: "1"
- Redness and pain on the palm of the hand and sole of the foot (palmar plantar erythrodysesthesia): "1"
- Fatigue/lack of energy (asthenia): "2
- Cough "4"
- Hoarse or Raspy or strained voice (dysphonia): "5"
- Diarrhea: "5"

The patient further commented that she believed that the benefits of the treatment outweighed the experience of the side effects, commenting as follows: *"It was worth all the side effects, trips to the Cancer Centre and change of life style."*

The patient was asked to explain why access to pembrolizumab+axitinib and future therapies are so important to her. She explained that pembrolizumab+axitinib resulted in significant bone tumour shrinking and that without this treatment, her condition would not have improved. The patient expressed a strong desire for continuing with future treatments that would improve her quality of life by enabling her to fulfill her social obligations of helping and caring for her loved ones.

In the CKUK survey, patients and caregivers were asked about the advantages of pembrolizumab+axitinib based on their experience. Two patients out of the 3 respondents of this question reported the advantages to be as follows: better control of the condition, short administration times and minimal, manageable side effects. One patient expressed optimism about future research and technologies helping better manage the disease.

One patient from the CKUK survey described their experience and the effect on quality of life, noting tolerable side effects.

"The only side effect I have experienced was some pneumonitis, which I believe is indicative of immunology. I suffered no shortness of breath, maybe a slight cough a day or so after my infusion. For me it is entirely tolerable, has no effect on my activities, I do a physical job, I go to the gym most days, I love to walk, and enjoy a pint! The lung inflammation only showed up on a CT scan, and was confirmed by chest x-ray. It has now subsided. Going to the hospital twice every 3 weeks is a little tedious (I have an oncology clinic on a Wednesday, and my infusion on the Friday) it takes about 90 mins by train door to door. My employer has been very accommodating..."

3.3 Companion Diagnostic Testing

N/A

3.4 Additional Information

Kidney Cancer provided pCODR with some additional guidance for determining the optimal sequencing of treatments following first-line treatment with pembrolizumab+axitinib. KCC strongly encourages pCODR to continuously consult prospective collection of real-world evidence on survival data, side effects and toxicities, cost-effectiveness and utilization. Additionally, pCODR is encouraged to continuously consult the Kidney Cancer Research Network of Canada for ongoing research regarding the optimal sequencing of treatments for renal cell carcinoma.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Place in therapy and sequencing with currently available treatments

Economic factors:

- Clarity on dosing schedule and treatment duration

Please see below for more details.

4.1 Currently Funded Treatments

For intermediate risk advanced or metastatic renal cell carcinoma (RCC), the current treatments are oral targeted therapies. Pazopanib and sunitinib are funded in all provinces for first-line treatment. Nivolumab plus ipilimumab was recently reviewed at pCODR and received a positive conditional recommendation for intermediate/poor risk patients with previously untreated, advanced or metastatic renal cell carcinoma.

For poor risk advanced or metastatic RCC, temsirolimus is also available but rarely used, in addition to pazopanib and sunitinib.

PAG noted that the KEYNOTE-426 trial compares pembrolizumab plus axitinib combination to sunitinib. PAG is seeking information on comparison to pazopanib and nivolumab plus ipilimumab or whether the trial results can be generalized to patients receiving other first-line therapies.

4.2 Eligible Patient Population

PAG is seeking clarity on the eligible patient populations. The reimbursement request is for patients with advanced RCC. KEYNOTE-426 trial included patients with clear cell histology and all IMDC prognostic risk groups and PD-L1 expression categories. PAG is seeking information on pembrolizumab plus axitinib in patients with non-clear cell histology or those with active CNS metastases. PAG is also seeking guidance on whether there are specific IMDC prognostic risk groups or PD-L1 expression categories where pembrolizumab plus axitinib is the preferred treatment in this setting.

PAG is seeking guidance on whether patients who have started first-line treatment (e.g., sunitinib, pazopanib, or nivolumab plus ipilimumab), and have not yet progressed or who are unable to tolerate treatment, could switch to pembrolizumab plus axitinib combination as their first-line treatment.

There is a potential for indication creep to previously treated patients (e.g., second-line treatment after treatment with first-line VEGF TKIs).

4.3 Implementation Factors

The dose is 200mg for RCC in the funding request and the KEYNOTE-426 trial. PAG noted trials suggest that weight based dose of 2mg/kg and 200mg fixed dose are similar. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight based dose for RCC (i.e., 2mg/kg up to 200mg) given the high cost of fixed dose compared to weight based dose for patients weighing less than 100kg. PAG also identified emerging data of dosing pembrolizumab at 400mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400mg or 4mg/kg up to a flat dose cap of 400mg every 6 weeks).

As pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. Familiarity with pembrolizumab administration is an enabler to implementation. However, vial sharing may not be feasible in smaller outpatient cancer centres. Furthermore, discontinuation of the 50 mg vial may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. PAG identified that the continued availability of the 50 mg vial by the manufacturer and introducing a 25 mg vial would be an enabler to implementation.

PAG is seeking clarity on treatment duration as in the KEYNOTE-426 trial treatment "continued until disease progression, development of unacceptable toxic effects, or physician or patient decision to discontinue" and treatment discontinuation. As pembrolizumab was administered for a maximum of 35 cycles in the KEYNOTE-426 trial, PAG is seeking clarity on whether patients should receive a total of two years of treatment or 35 cycles, as treatment interruptions due to toxicity may lead to two years occurring before 35 cycles are administered.

For patients who do not tolerate the pembrolizumab plus axitinib combination, PAG is seeking guidance on whether treatment with single agent pembrolizumab or single agent axitinib is appropriate.

As pembrolizumab is an intravenous therapy, whereas axitinib, pazopanib and sunitinib are oral therapies, PAG noted that additional pharmacy resources are required to prepare and administer the infusion, in addition to chemotherapy chair time and additional clinic visits. Incremental resources are required to monitor and treat infusion reactions, immune related adverse effects and other toxicities associated with immunotherapies.

Pembrolizumab, 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 in all jurisdictions for eligible patients, which is an enabler for patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of first-, second-, and third-line treatment with VEGF and PD-1 checkpoint inhibitors (e.g., pazopanib, sunitinib, nivolumab plus ipilimumab, and nivolumab) for IMDC risk groups (favourable, intermediate, and poor). In particular:

- Place in therapy for pembrolizumab plus axitinib and which patient population would benefit most from the combination and which patient population would be best suited for treatment with other available therapies.

- Treatment options after progression on pembrolizumab plus axitinib combination therapy (e.g., would nivolumab, another PD-1 inhibitor, be used in the second- or third-line setting?).
- Should patients who continue with single agent axitinib, after completing 35 cycles of pembrolizumab, be eligible for single agent nivolumab upon progression?

4.5 Companion Diagnostic Testing

PAG noted that the subgroup of patients with PD-L1 expression greater than 1% had better outcomes and is seeking clarity on whether PD-L1 testing is required. PD-L1 status is not currently being tested in renal cancer patients and is not required for use of nivolumab monotherapy in the second-line setting.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint input submission on behalf of three oncologists from Cancer Care Ontario and one joint submission on behalf of two oncologists from Kidney Cancer Research Network of Canada (KCRNC) were submitted for the review of pembrolizumab+axitinib for patients with advanced renal cell carcinoma (RCC). Based on the results of the KEYNOTE-426 trial, all clinicians agreed that pembrolizumab+axitinib would be a beneficial first-line combination therapy for previously untreated patients with advanced RCC, inclusive of all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups. All clinicians acknowledged that robust data on optimal sequencing of therapies is not currently available. A variety of possible sequencing options were presented by each clinician input based on current data and clinician practice. The clinicians noted that compared to sunitinib, pembrolizumab+axitinib showed a significantly longer overall survival (OS) and progression-free survival (PFS) as well as a higher objective response rate (ORR), with similar tolerance profiles.

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

5.1 Current Treatment(s) for Metastatic RCC

For intermediate risk advanced RCC, the current treatments are oral VEGFR targeted therapies. Pazopanib and sunitinib are funded in all provinces for first-line treatment. Nivolumab plus ipilimumab was recently reviewed at pCODR and received a positive conditional recommendation for intermediate/poor risk patients with previously untreated, advanced RCC.

5.2 Eligible Patient Population

Both clinician inputs agreed that pembrolizumab+axitinib would be an effective first-line combination regimen for patients with mRCC across all IMDC risk groups (favourable, intermediate and poor risk), as was observed in the KEYNOTE – 426 trial. Clinicians from KCRNC emphasized that it is particularly important that favourable risk patients have this therapy as an option because treating this population with sunitinib or pazopanib alone as a first-line treatment results in inferior OS.

5.3 Relevance to Clinical Practice

A clinician who had direct experience using pembrolizumab+axitinib from KCRNC noted that there are some patients that would be treated with pembrolizumab+axitinib over ipilimumab and nivolumab. For example, patients with favourable risk and patients where a rapid response is required. Achieving rapid response may be more predictable and achievable with an oral VEGFR targeted therapy (as part of a combination therapy) in the first 2-3 weeks. An example of a situation where a rapid response might be required is where there are vertebral/sacral metastases, a very vascular tumour and IV/C (inferior vena cava) right atrial thrombus causing cardiac symptoms.

Clinicians from KCRNC stated that at this time, it is unclear whether pembrolizumab+axitinib is a better treatment than ipilimumab and nivolumab. Clinicians from CCO stated that direct comparisons of pembrolizumab+axitinib versus nivolumab and ipilimumab are currently unavailable. However, pembrolizumab+axitinib would have an indication inclusive of a favourable risk population, whereas nivolumab and ipilimumab does not. Logistically, nivolumab and ipilimumab is administered for a maximum of 4 cycles, followed by nivolumab maintenance monotherapy. In contrast, pembrolizumab+axitinib is given as a combination until progression/intolerance (or up to 35 cycles of pembrolizumab). This combination regimen is different from other first line

VEGF-TKIs with respect to the addition of pembrolizumab+axitinib and has been shown to improve efficacy (overall survival), compared to a VEGF-TKI alone, while being tolerable. The side effect profile builds upon known safety signals with each drug.

Both groups of clinicians noted that contraindications of the pembrolizumab+axitinib combination would be in line with the known considerations for pembrolizumab or axitinib alone as per label, as well as sunitinib or an immunotherapy agent. Furthermore, input from KCRNC mentioned that in clinical practice, when used as single agents, PD-1 inhibitors have less high-grade toxicity than ipilimumab. In patients where the toxicities of ipilimumab are of concern, the treatment combination of pembrolizumab+axitinib may be preferred.

5.4 Sequencing and Priority of Treatments with Pembrolizumab

Both groups of clinicians noted that currently, there is no sufficient evidence to inform the optimal sequencing and priority of treatments with pembrolizumab+axitinib. Nonetheless, a few sequencing options were presented by clinicians. Pembrolizumab+axitinib would be used in the first-line treatment for patients with previously untreated advanced/metastatic RCC regardless of IMDC risk group. Some options for second-line treatments could include another VEGFR targeted therapy (post pembrolizumab+axitinib) or cabozantinib (following either pembrolizumab plus axitinib or ipilimumab and nivolumab).

Please see section 5.6: Implementation Questions for the responses to additional questions that the clinicians were asked on optimal sequencing.

5.5 Companion Diagnostic Testing

KCRNC specifically stated that testing for PDL-1 in RCC patients is not clinically relevant. Responses are seen in positive and negative tumor types.

5.6 Implementation Questions

5.6.1 Please consider the optimal sequencing of pembrolizumab plus axitinib with other treatment options (e.g., nivolumab plus ipilimumab, single agent nivolumab, pazopanib, and sunitinib), for the treatment of advanced RCC:

a. In what clinical scenarios (e.g., IMDC risk groups, PD-L1 status) would pembrolizumab plus axitinib or nivolumab plus ipilimumab or targeted therapies (e.g., pazopanib, sunitinib) be the preferred treatment for first-line RCC? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Both clinician inputs emphasized that the combination of pembrolizumab+axitinib would be used in patients with previously untreated advanced/metastatic RCC regardless of IMDC risk group. This combination would not replace nivolumab and ipilimumab, given that nivolumab and ipilimumab is indicated in IMDC intermediate and poor-risk patients. Clinicians from CCO further mentioned that mechanisms of actions differ and are non-redundant between the regimens: PD1+VEGF inhibition versus PD1+CTLA4 inhibition.

Both clinician inputs mentioned that currently, PDL-1 status does not play a role in choosing therapy. For patients deemed not eligible for any combination strategy, first line monotherapy TKIs should still be available for these scenarios. Clinicians from KCRNC further advised that patient preference is very important and may help determine

treatment choice in first-line setting when selecting between nivolumab and ipilimumab and pembrolizumab+axitinib, with relative toxicities being considered. Additionally, CRNC advised pCODR to consult the ongoing collection of real-world evidence to help determine the optimal sequencing of current and future treatment. See section 5.7 for more information of KCRNC's efforts to produce real-world data.

b. Is there evidence to inform sequencing of therapies following first-line pembrolizumab plus axitinib (e.g., would nivolumab, another PD-1 inhibitor, be used in the second- or third-line setting?)?

Clinicians from KCRNC commented that given the relatively small patient population requiring second and third-line treatments, very few head-to-head trials are expected and therefore the optimal sequencing of treatment for advanced RCC beyond first line is not clearly established. They further listed some considerations for sequencing as follows:

- Second-line treatment post pembrolizumab+axitinib: Treatment for patients who progress on a VEGFR targeted agent (eg. axitinib), there is data to support another VEGFR targeted therapy (phase III AXIS trial data).

- Second-line treatment (following either pembrolizumab plus axitinib or ipilimumab and nivolumab): Treatment with cabozantinib in this setting would be an option given its different mechanism of action (therapeutic MET and AXL inhibition). Note: Of the currently approved treatments available in Canada in the second and third line, cabozantinib shows significant improvement across all the key efficacy endpoints of OS, PFS and ORR.

Clinicians from CCO mentioned that although the optimal sequencing at this time is not entirely based on randomized data, the use of a monotherapy PD-1 inhibitor (i.e. nivolumab) immediately after progression during first line PD-1 combination phase with pembrolizumab+axitinib is not proven at this time.

c. Should patients who continue with single agent axitinib, after completing 35 cycles of pembrolizumab, be eligible for single agent nivolumab upon progression?

Clinician input from CCO mentioned that the re-initiation or repeat salvage use of PD-1/PD-L1 inhibitors in a delayed setting has been evaluated and is part of ongoing study (Lipson EJ et al. PMID: 23169436). This indicates a potential benefit of salvage, re-initiation of PD-1 inhibition in a clinical scenario of delayed progression on just axitinib, after having response/benefit to 35 cycles of pembrolizumab. Additionally, it is reasonable to use alternate treatments that have evidence in post VEGF-TKI setting (i.e Cabozantinib), immediately after the combination of Pembrolizumab/Axitinib (Lalani AA et al. PMID: 31237560).

Clinician input from KCRNC stated that many patients are currently coming off pembrolizumab after they received 35 cycles of treatment in the KEYNOTE-426 study. Data regarding those patients will become available in the future. Consideration must be given to the duration between stopping pembrolizumab and when disease progression occurs. If the duration between the final cycle of pembrolizumab and disease progression exceeds 6 months for example, another PD-1 inhibitor may have clinical efficacy. Data from other tumor sites, including KEYNOTE bladder studies, have demonstrated radiological evidence of tumor shrinkage following re-treatment with a PD-1 targeting agent (upon progression after completing treatment on a previous PD-1 targeting agent).

Additionally, KCRNC also commented that adding ipilimumab (targeting CTLA4) in patients progressing on nivolumab or pembrolizumab (targeting PD-1) would not be currently prescribed until further results and analysis.

5.6.2. Pembrolizumab was administered for a maximum of 35 cycles in the KEYNOTE-426 trial. Is there evidence with respect to treatment duration of pembrolizumab (i.e., 35 cycles versus 2 years maximum)? For example, treatment interruptions due to toxicity may lead to two years occurring before 35 cycles are administered.

Clinician input from CCO noted there is currently no available, robust prospective data comparing 35 cycles versus 2 years maximum. Both clinician groups noted that treatment administration should reflect the trial protocol to administer pembrolizumab for a maximum of 35 cycles.

5.7 Additional Information

KCRNC established a centralized database called the Canadian Kidney Cancer information system (CKCis) which collects prospective patient data from medical centres across Canada. CKCis is a flexible database can that can cater to a variety of different types of data needs to facilitate research on kidney cancer, including research to advise reimbursement decisions. KCRNC highlighted that CKCis was used to produce the first pCODR request for advice on funding axitinib as an alternative to everolimus for the second line treatment of mCRC. KCRNC also mentioned that the organization will be producing an updated consensus statement with treatment recommendations that reflect the available evidence at the time of the Canadian Kidney Cancer Forum (consensus conference) on April 13, 2019.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and effect of pembrolizumab in combination with axitinib on patient outcomes compared to appropriate comparators for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and will be outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs, conference abstracts, posters	Adult patients with advanced RCC that received pembrolizumab in combination with axitinib, as first-line treatment.	Pembrolizumab and axitinib	-SOC sunitinib -Nivolumab plus ipilimumab † -Pazopanib ‡	**-Overall Survival** **-Progression Free Survival** -Objective response rate -Duration of Response **-Safety** **-Quality of life** Potential Secondary Outcomes -Time to second line treatment (e.g., if subsequent treatment was started following first line treatment)

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
RCT: Randomized Control Trial; RCC: renal cell carcinoma; SOC: standard of care				

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

[†]Nivolumab +ipilimumab is for intermediate/poor risk patients with previously untreated, advanced or metastatic renal cell carcinoma

[‡]TKIs (pazopanib, sunitinib): intermediate risk

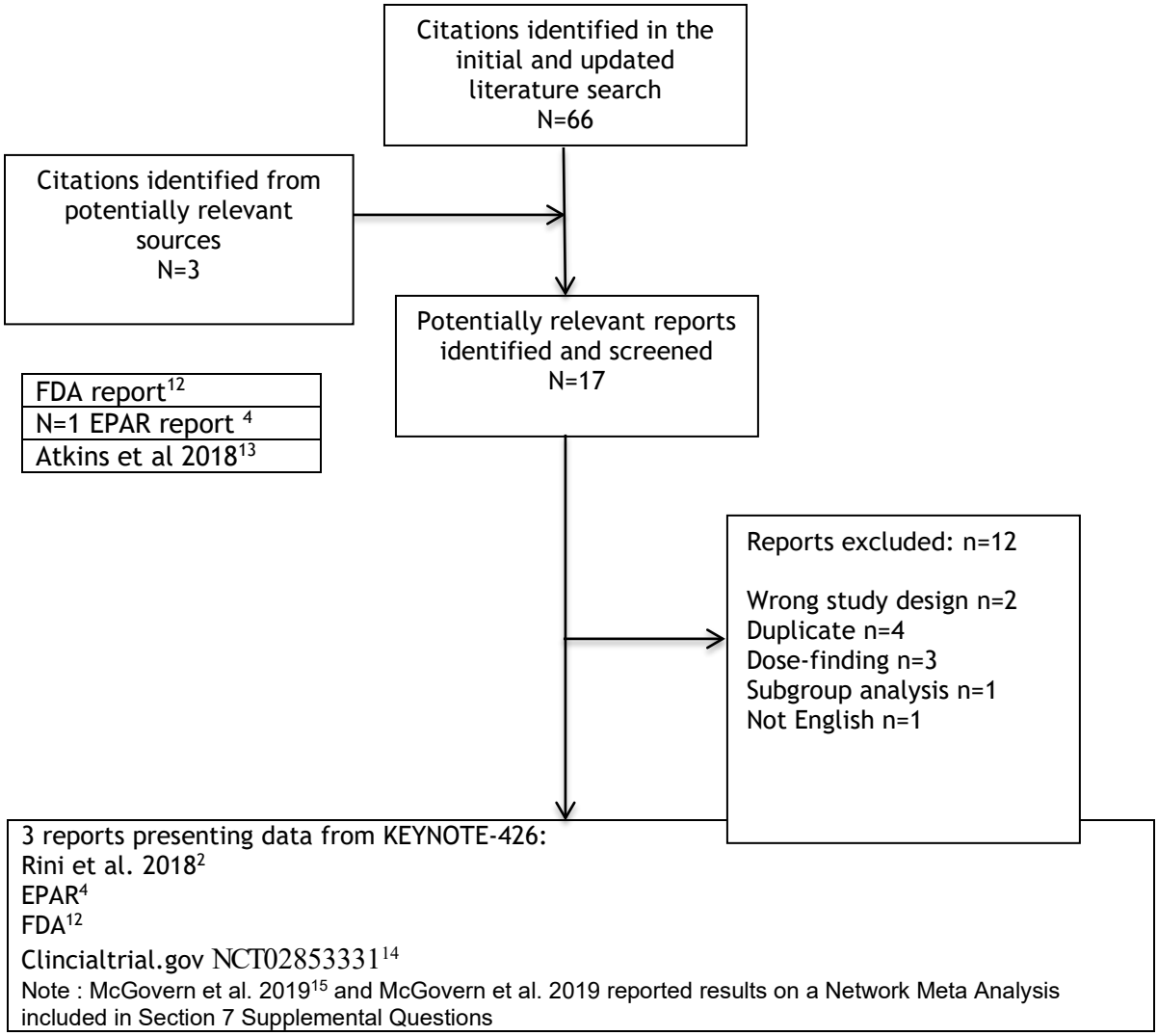
Poor risk: temsiroloimus available but rarely used

6.3 Results

6.3.1 Literature Search Results

Among the 15 potentially relevant reports identified by the search, one study[2] and two reports[4,12] were included in the pCODR systematic review and 12 studies were excluded.

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



Note: Additional data related to studies executive summary,[16] protocol,[2] clinical study report[5] *were also obtained through requests to the sponsor by pCODR*

6.3.2 Summary of Included Studies

One clinical trial KEYNOTE-426 was included in this systematic review. The key characteristics of this trial are summarized in table 4.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of KEYNOTE-426

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02853331 Phase III, ongoing open-label, multicenter, global randomized controlled trial. N=1062 patients screened and 861 patients randomized between October 24, 2016 and January 24, 2018 across 124 centers in 16 countries (4 sites across Canada). Funded by Merck Sharp & Dohme. Axitinib and sunitinib were provided by Pfizer. First interim analysis data cut off: August 24, 2018. Estimated Study Completion Date: January 27, 2022. According to the sponsor, the KN426 protocol specified second interim analyses (IA2) as post marketing commitment (PMC) and it will be available in August 2020. The protocol specified final analyses (FA) as PMC and it will be available in	Key Inclusion Criteria:[2] -Adults 18 years of age or older; -Newly diagnosed or recurrent stage IV (using the American Joint Commission on Cancer, seventh edition, classification) clear-cell renal-cell carcinoma; -No prior systemic therapy for advanced disease -Measurable disease per RECIST v1.1 -A tumour sample for biomarker assessment -≥1 measurable lesion according to RECIST v1.1 -Karnofsky performance-status score of ≥70 Key Exclusion Criteria:[2] -Symptomatic central nervous system metastases -Active autoimmune disease -Poorly controlled hypertension (systolic blood	Intervention[2] Pembrolizumab was administered intravenously at a dose of 200 mg once every 3 weeks. Axitinib was administered twice daily orally at a dose of 5 mg; the dose could be increased to 7 mg, then 10 mg, administered twice daily provided safety criteria were met and reduced to 3 mg, followed by 2 mg, administered twice daily to manage toxic effects. Sunitinib was administered orally at a dose of 50 mg daily for the first 4 weeks of each 6-week cycle; the dose could be reduced to 37.5	Co-Primary Outcome -Overall Survival-BICR - Progression Free Survival-BICR Secondary Outcomes -Objective response rate Duration of response Disease control rate Other -Patient reported outcomes -Global health status/quality of life EORTC QLQ-C30 - Time to deterioration based on the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease related symptoms (FKSI-DRS)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
September 2021.[3] According to the sponsor, EMA required more recent overall survival data for the proper assessment of the benefit/risk in all relevant subgroups.[6] Thus, an unplanned data cut off was available for January 2, 2019.[4]	pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg) -Ischemic cardiovascular event or New York Heart Association class III or IV congestive heart failure within 1 year before screening -Systemic immunosuppressive treatment	mg, then 25 mg, for the first 4 weeks of each 6-week cycle to manage toxic effects. Pembrolizumab was administered up to 35 cycles. <u>Comparators[2]</u> Sunitinib monotherapy administered 50 mg daily for the duration of 4 weeks and 2 weeks off	Safety
RCC renal cell carcinoma; RECIST Response Evaluation Criteria in Solid Tumors; BICR-Blinded Independent Central Review			

Table 5: Select quality characteristics of included studies of Pembrolizumab in combination with axitinib in patients with advanced RCC

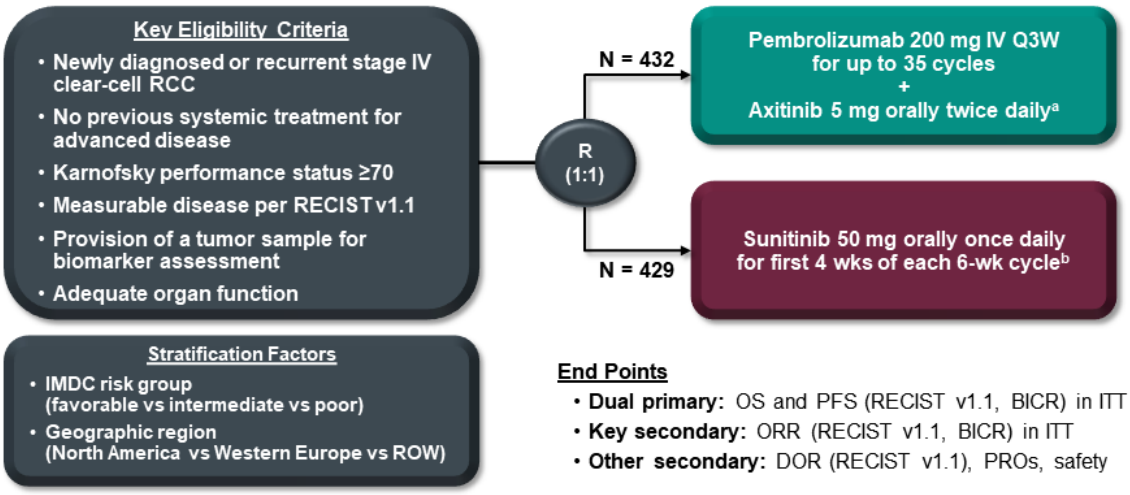
Study	KEYNOTE-426 trial NCT02853331
Treatment vs. Comparator	Pembrolizumab plus axitinib vs. sunitinib
Co-Primary outcomes	PFS OS
Required sample size	For the PFS endpoint, based on 380 events, the expected median PFS time in the sunitinib group is 11 months. The study is powered at 99% to obtain a HR=0.60 for pembrolizumab in combination with axitinib compared to sunitinib, alpha=0.2% (1 sided).[2] For the OS endpoint, based on 396 events, the expected median OS time in the sunitinib group is 29.3 months. The study is powered at 80% to obtain a HR=0.75 for pembrolizumab in combination with axitinib compared to sunitinib, alpha=2.3% (1 sided).[2]
Sample size	There were a total of 1062 participants screened and the first participant was screened on October 6, 2016. 861 participants were randomized in a 1:1 ratio with 432 patients in the pembrolizumab in combination with axitinib group compared to 429 patients in the sunitinib group.[4]

Randomization method	Each participant was stratified according to the following factors: 1) International mRCC Database Consortium (IMDC) risk categories (favourable vs. intermediate vs. poor) and 2) geographic regions (North America vs. Western Europe vs. "Rest of the World"). A patient's IMDC's risk category was determined by first assessing 6 risk factors: baseline Karnofsky Performance Status, Interval between diagnosis to start of first line systemic treatment, baseline hemoglobin, baseline platelet count, baseline corrected calcium, and baseline neutrophil.[4] Following stratification, participants were randomized in a 1:1 ratio using an interactive voice response system / integrated web response system (IVRS/IWRS)[2]
Blinding	Unblinded open label with a blinded independent radiologist review of responses.[4]
ITT Analysis	Yes
Ethics Approval	Yes
PFS: progression-free survival, OS: overall survival	

a) Trials

One open-label, multinational, phase III randomized controlled trial, KEYNOTE-426 met the inclusion criteria. This trial was funded by Merck Sharp & Dohme. Axitinib and sunitinib were provided by Pfizer. The aim of this trial was to examine the efficacy and safety of pembrolizumab plus axitinib compared to sunitinib in patients with advanced RCC.[2] The KEYNOTE-426 trial enrolled patients across 16 countries from 124 sites.[4] The country that enrolled the most patients was the United States (n=164) followed by Japan (n=94).[5] There were 43 patients from Canada. [5] During a maximum screening period of 28 days, patients deemed eligible were stratified according to the following factors: International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group (favourable, intermediate, or poor risk) and geographic region (North America, Western Europe, or rest of the world. Randomization was performed using an interactive voice response system / integrated web response system (IVRS/IWRS) in a 1:1 ratio to receive either pembrolizumab plus axitinib or sunitinib. [2] Key eligibility criteria included a histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features, locally advanced/metastatic disease, measurable disease according to RECIST v1.1, no prior systemic therapy received for advanced RCC, KPS ≥ 70%, bone metastases treatment should have been initiated 2 weeks prior to randomization and patients should have functioning organs. [4] Crossover was not permitted in the KEYNOTE-426 trial.[3] Figure 1 illustrates the study design.

Figure 1. Study design[16]



Screening

Prior to conducting protocol-specific procedures, informed consent was received.[2] The duration of screening was 28 days prior to randomization. In the event a patient did not meet the initial inclusion/exclusion criteria, he/she was considered for rescreening based on consultation with the Sponsor. Safety assessments (e.g., laboratory tests, ECG, vital signs and evaluation of KPS) were conducted 10 days in advance of randomization. A pregnancy test was conducted 72 hours prior to the first dose of treatment among women of child bearing age.[2]

Treatment Period

Patients randomized in the pembrolizumab and axitinib group who discontinued pembrolizumab due to stable disease or better were eligible for up to 17 additional infusions of pembrolizumab in the event they progressed after stopping treatment. In order to qualify for re-treatment (i.e., second course phase), the following conditions had to have been met:[2]

- Discontinued initial treatment with pembrolizumab following confirmed CR based on RECIST 1.1-investigator assessed and received a minimum of 8 doses of pembrolizumab

  OR

- Finished roughly 2 years of treatment with pembrolizumab and did not experience progressive disease

  AND

- Following discontinuation of initial treatment with pembrolizumab, experienced an investigator-confirmed radiographic disease progression

- No anti-cancer treatment from the time of the last dose of pembrolizumab
- KPS of ≥ 70%
- No history or evidence of condition, therapy or laboratory abnormality that may have impacted the patient's enrollment for the complete duration of the trial or considered not in favour of the patient to participate based on the discretion of the treating investigator
- Adequate organ function

The sponsor noted that as of December 5, 2019, 8 subjects were enrolled in the second course retreatment phase. One of these subjects, already had PD and has been discontinued; however, there were 7 subjects still currently enrolled in second course.[17]

Post-Treatment
The end of treatment visit was expected to occur at the time study treatment was discontinued. Patients who may have discontinued treatment for reasons other than disease progression were considered to be part of the study and expected to resume scheduled assessments.[2]

Safety Follow-up Visit
Roughly 30 days (+/- 3 days) after the last dose of trial treatment or before a new anti-cancer treatment was initiated (if this occurs prior to 30 days after the last dose of study treatments), a compulsory safety follow-up visit was conducted.[2]

Imaging Follow-up Visits
Imaging assessments as scheduled were performed unless the following events occurred in the following order [2]

1) PD is BICR verified
2) a new anti-cancer treatment commenced
3) death
4) withdrawal of consent or
5) study conclusion or early termination, whichever occurred first.

Outcomes and Disease Assessment
The co-primary efficacy endpoints of KEYNOTE-426 were overall survival defined as the time from randomization to death from any cause as well as progression-free survival defined as the time from randomization to disease progression according to RECIST based on blinded independent central review or death from any cause.[2]

Secondary outcomes included the following:

The key secondary outcome was objective response rate (ORR) defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR) per RECIST 1.1. [2]

Duration of response (DOR) according to RECIST 1.1 by BICR for subjects who demonstrate CR or PR defined as the time from first documented evidence of CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. [2] Additionally, disease control rate (DCR) according to RECIST 1.1 by BICR defined as the percentage of subjects who have achieved CR, PR, or stable disease (SD) of ≥ 6 months per RECIST 1.1.[5]Data on patient reported outcomes including physical function and health-related quality of life was captured. [2]

Functional assessment of Cancer Therapy Kidney Symptom Index—Disease-Related symptoms (FKSI-DRS) is a patient-reported instrument that measures whether the patient

has experienced any of the following 9 kidney cancer-related symptoms: lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, or blood in the urine. Summary symptom scores range from 0 to 36, with higher scores that reflect improved symptom status. [2]A minimum change of at least 2 points on the FKSI-DRS scale was used to define symptom progression in other mRCCC trials. [16 7]

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) encompasses 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores ranges from 0-100 and higher scores represent higher response level: Either worse symptoms, better function, or better HRQoL. A clinically meaningful change from baseline was defined as a ≥ 10-point change within a treatment arm.[2]

The EuroQol EQ-5D-3L was used to provide data for use in economic models and analyses. The following are health state dimensions included in the EuroQol EQ-5D-3L: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A three-point scale was used for each dimension ranging from 1 (extreme problem) to 3 (no problem). Patients rated general state of health at the time of the assessment on a scale of 0 to 100 on the visual analog scale included within the EuroQol EQ-5D-3L. [2]

Safety was reported using the as-treated safety population defined as patients randomly assigned who received one or more doses of trial treatment. Data on serious adverse events was collected for 90 days following the end of the treatment period and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[2]

Sample Size and Statistical analysis

The co-primary endpoints were assessed in the ITT population. The non-parametric Kaplan-Meier method was applied in order to determine the PFS curve and survival curves in the pembrolizumab and axitinib group and sunitinib group. The stratified log-rank test was used to assess treatment difference in PFS. A stratified Cox proportional hazard model with Efron's method of tie handling was conducted to obtain the treatment difference (i.e., HR) and 95% confidence interval between the pembrolizumab and axitinib group compared to sunitinib group. The aforementioned stratification factors used for randomization were accounted for in the stratified log-rank test and the stratified Cox model. [2]

For the PFS endpoint, a target number of 487 PFS events and one interim analysis at approximately 75% of the target number of events has approximately 99% power to generate an HR=0.60, alpha =0.2% (1-sided).[4] The projected number of PFS events for the first and second interim analysis are expected at 22 and 31 months, respectively. For the OS endpoint, a target number of 404 final OS events and two interim analyses (roughly 48% of final OS events at the first interim analysis and 74% of the final OS events at the second interim analysis) approximately 80% power to generate an HR=0.75, alpha =2.3% (1-sided). The projected number of OS events for the first and second interim analysis are expected at 22 and 31 months respectively.[4]

For the outcomes of objective response rate and disease control rate and the comparison between the pembrolizumab and axitinib versus sunitinib, stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used. Similar to PFS and OS, stratification factors will be accounted for in the stratified log-rank test and the stratified Cox model. [2]

Similar to PFS and OS, the non-parametric Kaplan-Meier method was used to estimate the DOR curve in each treatment group. The proportion of patients still in response and 95% CIs at specific duration time points were provided.[4]

Two sensitivity analyse were performed to investigate the robustness of the PFS endpoint according to RECIST v1.1 by BICR each with different censoring rules.[2] Table 6 outlines the censoring rules applied.

Table 6. Censoring rules for primary and sensitivity analyses of PFS[4]

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

PD = progressive disease; PFS = progression-free survival.

The study outlined two interim analyses for OS and one interim analysis for PFS.[4] Approximately 305 PFS events were needed to proceed with the interim analysis. The second interim analysis was targeted when approximately 74% of the final required OS events (or 299 deaths) have occurred which was projected after 31 months from study commencement. The final OS analysis was conducted provided the target number of OS events (404 deaths) is achieved which was expected at 43 months after the start of the study, given the study has not already been stopped. [2] According to the Sponsor, the protocol specified second interim analyses (IA2) as post marketing commitment (PMC) will

be available in August 2020. The protocol specified final analyses (FA) as PMC will be available in September 2021.[3]

If superiority of PFS was demonstrated in the first interim analysis however superiority of OS was not achieved (without crossing the futility boundary for OS), the study was to resume for OS after the interim analysis.[2] For PFS, the one-sided p value threshold identified for superiority of pembrolizumab and axitinib over sunitinib was 0.0013 where as for OS, the one-sided p value threshold identified for superiority of pembrolizumab and axitinib over sunitinib was 0.0001. [2]
If superiority of pembrolizumab in combination with axitinib relative to sunitinib for the co-primary endpoints of PFS or OS was reached at the first interim analysis, testing for ORR was performed with the overall Type I error alpha=0.1%, 1.2%, or 2.5%, depending on the results of the OS and PFS tests.[2]

A multiplicity strategy using the Maurer and Bretz approach was applied for the following hypotheses: superiority of the pembrolizumab and axitinib compared to sunitinib on PFS or OS) and the superiority of pembrolizumab and axitinib versus to sunitinib in ORR. Type 1 error assessed the outcomes of OS, PFS and ORR will be controlled at alpha=2.5% (1-sided) with 0.2% assigned to PFS and 2.3% allocated to OS. Success was achieved if either PFS or OS was found statistically significant under multiplicity control.[4] Figure 2 outlines the multiplicity strategy. Table 7 outlines the interim and final analyses strategies.

Figure 2. Maurer and Bretz Multiplicity Strategy[4]

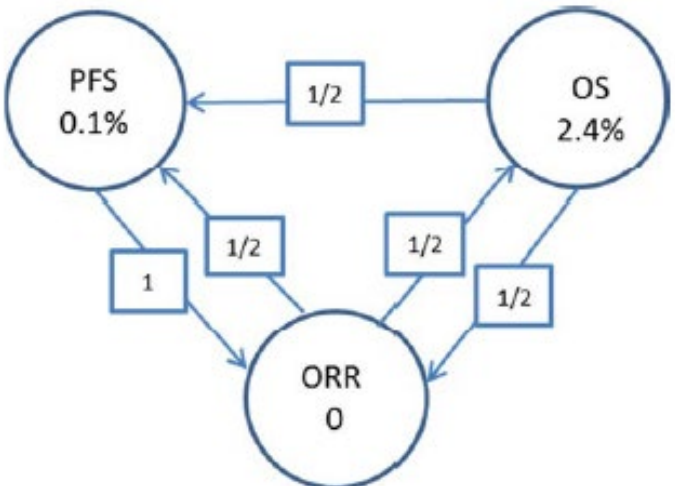


Table 7. Summary of interim and final analyses[4]

Analysis	Expected Months after Study Start	Hypothesis Tested in the Analysis	True Hazard Ratio	n[†]	Information Fraction	Type I Error (Overall α)	Efficacy Boundary Crossing				Futility Boundary Crossing			
							Nominal α	Z-value	Statistics[‡]	Power[§]	Nominal α	Z-value	Hazard Ratio	Cumulative Type II Error
IA1	22 Months	PFS	0.6	365	0.75	0.20%	0.11%	3.06	0.73	~96.5%	22.1%	-0.77	1.08	<0.01%
						1.35%	0.74%	2.44	0.77	~99.2%	21.8%	-0.78	1.08	<0.01%
						2.5%	1.36%	2.21	0.79	~99.6%	21.6%	-0.79	1.08	<0.01%
		OS	0.75	195	0.48	2.3%	0.01%	3.72	0.59	~4.3%	4.1%	-1.74	1.28	~0.01%
						2.5%	0.01%	3.70	0.59	~4.5%	4.1%	-1.74	1.28	~0.01%
		ORR	-	860	1.0	0.2%	0.2%	2.88	9.4%	>99.9%	-	-	-	-
						1.15%	1.15%	2.27	7.4%	>99.9%				
						2.5%	2.5%	1.96	6.4%	>99.9%				
IA2	31 Months	PFS	0.6	487	1.0	0.2%	0.14%	3.00	0.76	>99.9%	99.8%	3.00	0.76	~3.9%
						1.35%	1.02%	2.32	0.81	>99.9%	98.7%	2.32	0.81	~0.04%
						2.5%	1.95%	2.06	0.83	>99.9%	97.5%	2.06	0.83	~0.02%
		OS	0.75	299	0.74	2.3%	0.78%	2.42	0.76	~52.7%	20.3%	-0.84	1.10	~0.05%
						2.5%	0.92%	2.36	0.76	~55.1%	20.2%	-0.85	1.10	~0.05%
FA	43 Months	OS	0.75	404	1.0	2.3%	2.07%	2.04	0.82	~80.8%	97.7%	2.04	~0.82	~19.2%
						2.5%	2.22%	2.01	0.82	~81.7%	97.5%	2.01	~0.82	~18.3%

[†] n means expected events at the time of corresponding analysis for PFS and OS based on model assumption. In the rare case if PFS events accumulate slower than expected, a minimum of 305 events is required at 22 months to trigger IA1; n means total sample size for ORR.

[‡] The statistics used here are hazard ratio for PFS and OS, and ORR Δ for ORR where ORR Δ = ORR in (pembrolizumab+axitinib group) – ORR in sunitinib group.

[§] The power calculated for OS is cumulative power. For the power calculation, the target ORR in the pembrolizuab+axitinib group and the reference ORR assumed in the sunitinib groups are 55% and 31%, respectively.

For OS, a linear spending function with a fixed alpha spending of 0.0001 at IA1 and the rest alpha spending approximated by a Hwang-Shih-DeCani (HSD) alpha-spending function with gamma parameter (-4) is used to construct Haybittle-Peto type of group sequential boundaries to control the overall Type I error rate for this endpoint at 2.3% or 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at IA2 and FA will be determined by the spending function evaluated at the exact number of deaths at each analysis.

For PFS, an HSD alpha-spending function with gamma parameter (-2), is used to construct group sequential boundaries to control the overall Type I error rate for this endpoint at 0.2%, 1.35% and 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at the interim analysis will be determined by the spending function evaluated at the exact number of PFS events at each analysis.

For ORR, if the testing of ORR hypothesis does not reach statistical significance at interim analysis 1 (IA1), the p-value from the IA1 analysis can be compared to an updated α-level if the null hypothesis for PFS or OS is rejected at a later time.

Objective response rate was tested at a one-sided p value of 0.025 provided the PFS and OS thresholds were met.[2]

Safety results were assessed using a tiered approach. There are no tier 1 events. Point estimates and corresponding 95% CIs were provided for comparisons between pembrolizumab and axitinib versus sunitinib. Safety events were classified as tier 2 or tier 3 based on the number of events observed. An adverse event that has been experienced by at least 4 patients was identified tier 2 with all other events with a predefined limit as tier 3. [2]Table 8 outlines the analysis strategy for safety parameters.

Table 8. Analysis strategy for Safety Parameters[2]

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any Serious AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Any Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific AEs or SOCs (incidence ≥10% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Serious AE (incidence <5% of subjects in one of the treatment groups)		X
	Any Grade 3-5 AE (incidence <5% of subjects in one of the treatment groups)		X
	Any Serious and Drug-related AE		X
	Any Grade 3-5 and Drug-related AE		X
	Dose Modification due to AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs or SOCs (incidence <10% of subjects in all of the treatment groups) or PDLCs		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

Abbreviations: AE = adverse event; CI = confidence interval; ECG = electrocardiogram; PDLC = pre-defined limit of change; SOC = system organ class.

Subgroup analyses to determine the between group treatment effect (95% CI) were outlined for the following classification variables: IMDC risk category, geographic region, PD-L1 status, age, sex and race.[2] According to the Sponsor, no pre-specified interaction test for subgroup analyses were performed as no interaction effect between subgroups were expected at study design stage.[3]

Important protocol deviations were defined as deviations that may significantly impact the quality of the study including the completeness, accuracy and reliability or integrity of the data or affect a participant's rights, safety or well-being. The proportion of important protocol deviations were approximately similar (14.2% in the pembrolizumab and axitinib group and 12.9% in the sunitinib group). Deviations occurred in the following categories: discontinuation criteria, inclusion/exclusion, informed consent form, prohibited medications, safety reporting, study intervention and trial procedures. One protocol deviation was identified as clinically significant. An SAE (peritonitis) was observed in one patient in the pembrolizumab and axitinib group that the Sponsor was made aware of more than 90 days following when the SAE occurred. This patient was not excluded from any analyses and the SAE was handled with no action taken regarding study treatment and the patient continued in the study. [4]

There were 2 patients in the pembrolizumab and axitinib group that received prohibited medications (i.e., "Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment (unless allowed per protocol)." In contrast, the patients in the sunitinib arm received a drug having a pro-arrhythmic potential. The proportion of patients that received "2 consecutive Imaging Scans up to week 54 or 1 imaging scan after Week 54, not performed for all anatomical locations required or missed entirely" was 5.1% in the pembrolizumab and axitinib group compared to 4% in the sunitinib arm.[4]

There were 6 total protocol amendments (global and 2 country-specific amendments). There were 7 protocol versions in addition to the original protocol. Highlights of the main protocol

amendments are outlined in Table 9. The sponsor noted that these protocol amendments did not impact the overall results of the trial.[6]

Table 9. Summary of main protocol amendments[4]

Protocol Amendment	Most relevant changes
#01 (21 July 2016)	Country specific (Japan)
#2 (3 October 2016)	Country specific (France)
# 3 (13 Mar 2017)	First Global Amendment - Inclusion criteria: changed the allowed time period for starting bone resorptive therapy from 4 weeks to 2 weeks prior to randomization. - Exclusion criteria: clarify that subjects who have had chemotherapy as neoadjuvant or adjuvant therapy for RCC qualify for the study. - Exclusion criteria: revised the timeframe of active autoimmune disease exclusion from 3 months to 2 years. Added language on excluded therapies and allowed replacement therapies. - Exclusion criteria: clarify that subjects with brain metastasis who have been treated with steroid treatment at least 14 days (changed "4 weeks" to "14 days") prior to randomization in order to show stability qualify for the study. - Exclusion criteria: exclude subjects with a known history of hepatitis B. - Exclusion criteria: removal of exclusion for "GI perforation": repaired GI perforation is not excluded.
#4 (21 Mar 2017)	Country specific (Japan) version of global amendment #3
#5 (21 Mar 2017)	Country specific (France) version of global amendment #3
#8 (28 August 2017)	Second Global Amendment To further refine general guidance on evaluation and management of overlapping AEs potentially associated with either pembrolizumab and axitinib or both in the combination arm and include a new subsection detailing evaluation and management of transaminase elevations during axitinib and pembrolizumab combination therapy (Section 5.2.2.3). The rational for this change was to provide detailed guidelines on how to systemically approach treatment–emergent alanine aminotransferase [ALT]/aspartate aminotransferase [AST] elevations in the pembrolizumab + axitinib group as there are no specific markers to differentiate drug-induced liver injury from axitinib versus immune-mediated hepatitis from pembrolizumab versus ALT/AST elevations due to other reasons. The amedment also provided detailed algorithms regarding study drug rechallenge for different scenarios following recovery from an initial ALT/AST elevation event.
#9 (07 September 2017)	Country specific (France) version of global amendment #8

Table 9. Summary of main protocol amendments continued [4]

#10 (19 October 2017)	Third Global Amendment The primary reason for the amendment was to revise Table 6 in Section 5.2.2.1 (Dose Modification and Toxicity Management Guidelines for Adverse Events Potentially Associated with Pembrolizumab Treatment), to include: 1) myocarditis as a new immunerelated AE (irAE); and 2) under all the "other immune-related AEs" , any Grade 3 AE was separated from intolerable Grade 2 as a standalone category. These updates were required to be consistent with the guidelines provided in the IB and product label that were current at that time.
#11 (26 October 2017)	Country specific (France) version of global amendment #10
#12 (03 May 2018)	Fourth Global Amendment - Statistical Analysis Plan: 1) Revised assumptions on control arm median PFS and OS 2) Revised IA1 trigger from 50% final OS events to once achieving 305 PFS events and 7 months of minimum follow up. 3) Added one interim analysis for PFS to have earlier chance of observing positive efficacy of PFS with relatively mature data. 4) Initial alpha to PFS and OS changed from 0.1% and 2.4% to 0.2% and 2.3% respectively. Slightly higher alpha is reallocated to PFS to ensure adequate power for this important primary endpoint without compromising the power of OS 5) Secondary objectives: landmark analyses on PFS and OS are added to compare and characterize the tail of the curve (PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months, and OS rates at 12, 18, and 24 months, based on data adequacy). 6) Updated the censoring rules for primary and sensitivity analyses of PFS.
#13 (11 May 2018)	Country specific (France) version of global amendment #12

Note: There was only 1 country-specific protocol amendment for Japan, which was protocol amendment 426-01. Protocol amendment 426-04 was global amendment 426-03 with changes from 426-01 carried over.
There was only 1 country-specific protocol amendment for France, which was amendment 426-02. Protocol amendments 426-05, -09, -11 and -13 were global amendments 426-03, -08, -10 and -12 with changes from 426-02 carried over.

The first interim analysis occurred at the data cut off August 24, 2018. The median duration of follow up was 13.2 months (range: 0.1-21.5 months) in the pembrolizumab and axitinib group and 12.1 months (range: 0.4-22.0 months) in the sunitinib group. [4] The sponsor clarified that the EMA required more recent OS data for the proper assessment of the benefit/risk in all relevant subgroups. Therefore, an unplanned analysis was conducted with a data cut off of January 2, 2019.[6] The median follow-up in the ITT population was 17.4 months (range: 0.1-25.6) in pembrolizumab and axitinib arm, and 15.7 months (range: 0.4-26.3) in the sunitinib arm. [4] The number of patients in the ITT population was 861 (432 patients in the pembrolizumab and axitinib group vs 429 patients in the sunitinib group). The number of patients in the ASaT population (that received treatment) was 854 patients (429 patients in the pembrolizumab and axitinib group vs. 425 patients in the sunitinib group).[4]

a) *Populations*

KEYNOTE-426 randomized 432 patients to the pembrolizumab plus axitinib group and 429 patients to the sunitinib group. According to the study authors, the baseline patient characteristics were well balanced in the pembrolizumab plus axitinib group and sunitinib group. The median age was 62 years (range: 30-89) and 61 years (range: 26-90) in the pembrolizumab plus axitinib and sunitinib group, respectively. The most common site of metastases was the lung among 312 patients (72.2%) and 309 patients (72.0%) in the pembrolizumab plus axitinib and sunitinib group respectively.[2] The patient demographics and baseline disease characteristics of all enrolled patients in the intention-to-treat population (ITT) are presented in Table 10.

Table 10: Patient demographics and baseline disease characteristics of the ITT population[2]

Characteristic	Pembrolizumab–Axitinib (N=432)	Sunitinib (N=429)
Age		
Median (range) — yr	62 (30–89)	61 (26–90)
<65 yr — no. (%)	260 (60.2)	278 (64.8)
Male sex — no. (%)	308 (71.3)	320 (74.6)
Region of enrollment — no. (%)		
North America	104 (24.1)	103 (24.0)
Western Europe	106 (24.5)	104 (24.2)
Rest of the world	222 (51.4)	222 (51.7)
IMDC prognostic risk — no. (%)†		
Favorable	138 (31.9)	131 (30.5)
Intermediate	238 (55.1)	246 (57.3)
Poor	56 (13.0)	52 (12.1)
Sarcomatoid features — no./total no. with known status (%)	51/285 (17.9)	54/293 (18.4)
PD-L1 combined positive score — no./total no. with data (%)‡		
≥1	243/410 (59.3)	254/412 (61.7)
<1	167/410 (40.7)	158/412 (38.3)
No. of organs with metastases — no. (%)§		
1	114 (26.4)	96 (22.4)
≥2	315 (72.9)	331 (77.2)
Most common sites of metastasis — no. (%)¶		
Lung	312 (72.2)	309 (72.0)
Lymph node	199 (46.1)	197 (45.9)
Bone	103 (23.8)	103 (24.0)
Adrenal gland	67 (15.5)	76 (17.7)
Liver	66 (15.3)	71 (16.6)
Previous radiotherapy — no. (%)	41 (9.5)	40 (9.3)
Previous nephrectomy — no. (%)	357 (82.6)	358 (83.4)

* There were no significant differences between groups, at a two-sided alpha level of 0.05. Percentages may not total 100 because of rounding.

† Favorable risk corresponds to an International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score of 0, intermediate risk to a score of 1 or 2, and poor risk to a score of 3 to 6. IMDC risk score is determined by the total number of the following six risk factors that are present: Karnofsky performance-status score of less than 80 (on a scale from 0 to 100, with lower scores indicating greater disability[12]), a time from initial diagnosis to randomization of less than 1 year, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium level above the upper limit of the normal range, an absolute neutrophil count above the upper limit of the normal range, and platelet count above the upper limit of the normal range.[14]

‡ The programmed death ligand 1 (PD-L1) combined positive score was calculated as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells, multiplied by 100.

§ Information on the number of organs with target and nontarget lesions was missing for three patients (0.7%) in the pembrolizumab–axitinib group and for two patients (0.5%) in the sunitinib group.

¶ A post hoc Stouffer's test, which tests for imbalances between groups, suggested that random assignment resulted in near-perfect balance between treatment groups in the sites of metastasis. A review of randomization procedures did not reveal any aberrations.

Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

b) ***Interventions***

Pembrolizumab was intravenously administered as 200 mg every 3 weeks in combination with axitinib which was orally administered 5 mg twice daily. For patients that received pembrolizumab plus axitinib, dose modification was accepted independently for the two drugs. While the starting dose of axitinib is 5 mg, a dose reduction was provided at 3 mg BID followed by 2 mg BID if required. If 2 mg cannot be tolerated by the patient, axitinib should be permanently discontinued. [2] The duration of treatment for pembrolizumab was up to 35 doses (about 24 months) or until disease progression is verified or further confirmed by the investigator.[2] When axitinib is administered in combination with pembrolizumab, dose escalation of axitinib above the 5 mg dose is permitted at intervals of 6 weeks or longer .[12]

Sunitinib was orally administered 50 mg once daily for the first 4 weeks of a 6 week cycle.[2] In the event of toxic effects, the dose could be reduced to 37.5 mg, then 25 mg, for the first 4 weeks of each 6-week cycle. If one drug in the pembrolizumab–axitinib group was discontinued because of toxic effects, the other drug could be continued.[2] Eighty-nine patients (20.7%) from the pembrolizumab and axitinib group discontinued pembrolizumab and continued axitinib, while 88 (20.5%) patients discontinued axitinib and continued pembrolizumab monotherapy.[3] Per study protocol participants could continue pembrolizumab until 2 years after randomization, while participants could continue axitinib until PD or toxicity.[3]

In their feedback on the pERC initial recommendation, the Provincial Advisory Group (PAG) noted that the duration of therapy of pembrolizumab should align with the Keynote-426 trial. PAG noted that they disagreed with the recommendation regarding 35 cycles of pembrolizumab.

The Keynote-426 trial protocol states that treatment with pembrolizumab will be administered for a maximum of 35 doses (approximately 2 years).[18] If a patient remains progression-free after 35 doses of pembrolizumab, treatment with axitinib will be continued as monotherapy until PD is BICR verified or further confirmed by the investigator. In addition, if 1 of the 2 drugs needs to be discontinued because of toxicity or intolerance, treatment with the other drugs as monotherapy will be continued until PD is BICR verified or further confirmed by the investigator. Patients who stop pembrolizumab after 35 doses without PD or stop pembrolizumab due to having achieved a CR may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses (approximately 1 year) upon experiencing PD.[18] Due to the different toxicity profiles associated with pembrolizumab, axitinib and sunitinib, dose modification guidelines for possible adverse events associated with pembrolizumab and axitinib treatment were outlined.[18]

In the event of a medical/surgical event, dose interruptions were allowed for pembrolizumab. If drug-related toxicity is considered associated with pembrolizumab and dose modification is required, pembrolizumab dosing will be held until re-treatment criteria is met. Delays for up to 12 weeks between pembrolizumab doses due to toxicity were permitted.[2]

There were 98.6% of participants in the pembrolizumab in combination with axitinib group and 99.3% of participants in the sunitinib group that received concomitant medications. Analgesics, agents acting on the renin-angiotensin system, and drugs for acid-related disorders were classified as being the most

frequently used concomitant medications in >50% of participants in 1 or more treatment groups. There were 47.8% of participants in the pembrolizumab plus axitinib group and 20.7% of participants in the sunitinib group that reported use of systemic corticosteroids.[5] There were no contraindications.[12]

In the ITT population, there were 88 patients (20.4%) in the pembrolizumab in combination with axitinib group that received any subsequent anticancer therapy compared to 147 patients (34.3%) in the sunitinib group. Specifically, 8 patients (1.9%) in the pembrolizumab and axitinib group received a PD-1 or PD-L1 inhibitor. Nivolumab was the most common PD-1 or PD-L1 inhibitor used by 8 patients (1.9%) in the pembrolizumab and axitinib group compared with 88 patients (20.5%) in the sunitinib group. Any VEGF or VEGFR inhibitor was used by 78 patients (18.1%) in the pembrolizumab and axitinib group compared with 86 patients (20.0%) in the axitinib group. Cabozantinib was used by 33 patients (7.6%) in the pembrolizumab and axitinib group versus 22 patients (5.1%) in the sunitinib group. Sunitinib was used by 29 patients (6.7%) in the pembrolizumab and axitinib group compared with 18 patients (4.2%) in the sunitinib group. Details are outlined in Table 11.

Table 11. Summary of Subsequent Anticancer Therapy[2]

Therapy, n (%)	Intention-to-Treat Population		Patients Who Discontinued Study Treatment	
	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)	Pembrolizumab + Axitinib (N=176)	Sunitinib (N=242)
Any	88 (20.4)	147 (34.3)	88 (50.0)	147 (60.7)
Any PD-1 or PD-L1 inhibitor	8 (1.9)	91 (21.2)	8 (4.5)	91 (37.6)
Atezolizumab	0	1 (0.2)	0	1 (0.4)
Durvalumab	0	2 (0.5)	0	2 (0.8)
Nivolumab	8 (1.9)	88 (20.5)	8 (4.5)	88 (36.4)
Pembrolizumab	0	1 (0.2)	0	1 (0.4)
Any VEGF or VEGFR inhibitor	78 (18.1)	86 (20.0)	78 (44.3)	86 (35.5)
Axitinib	7 (1.6)	28 (6.5)	7 (4.0)	28 (11.6)
Bevacizumab	0	1 (0.2)	0	1 (0.4)
Cabozantinib	33 (7.6)	22 (5.1)	33 (18.8)	22 (9.1)
Lenvatinib	9 (2.1)	5 (1.2)	9 (5.1)	5 (2.1)
Pazopanib	13 (3.0)	21 (4.9)	13 (7.4)	21 (8.7)
Sorafenib	0	2 (0.5)	0	2 (0.8)
Sunitinib	29 (6.7)	18 (4.2)	29 (16.5)	18 (7.4)
Other	21 (4.9)	26 (6.1)	21 (11.9)	26 (10.7)
Everolimus	16 (3.7)	14 (3.3)	16 (9.1)	14 (5.8)
Glutaminase inhibitor (unspecified)	2 (0.5)	2 (0.5)	2 (1.1)	2 (0.8)
Hypoxia inducible factor 2 alpha inhibitor (unspecified)	1 (0.2)	0	1 (0.6)	0
Ibrutinib	0	1 (0.2)	0	1 (0.4)
Interferon (unspecified)	3 (0.7)	2 (0.5)	3 (1.7)	2 (0.8)
Interferon alfa-2a	0	1 (0.2)	0	1 (0.4)
Interferon gamma	1 (0.2)	0	1 (0.6)	0
Investigational drug (unspecified)	0	2 (0.5)	0	2 (0.8)
Ipilimumab	2 (0.5)	6 (1.4)	2 (1.1)	6 (2.5)
Savolitinib	0	1 (0.2)	0	1 (0.4)
Vinblastine	2 (0.5)	0	2 (1.1)	0

Patients may have received more than one subsequent therapy overall and within each category.

Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

In the pembrolizumab plus axitinib group, the median duration of any treatment was 10.4 months (range: 0.03-21.2) compared to 7.8 months (range: 0.07-20.5) in the sunitinib group. In the pembrolizumab plus axitinib group, the median duration

of treatment was 8.3 months with pembrolizumab plus axitinib, 9.2 months with pembrolizumab and 9.6 months with axitinib.[2]

According to the protocol, patients with unconfirmed disease progression who were in clinically stable condition could continue to receive treatment at the discretion of the investigator. 120 patients in total (59 subjects on the pembrolizumab and axitinib arm and 61 patients on the sunitinib arm, respectively) had unconfirmed disease progression by IRC at initial verification of progression (VOP) request. [3]

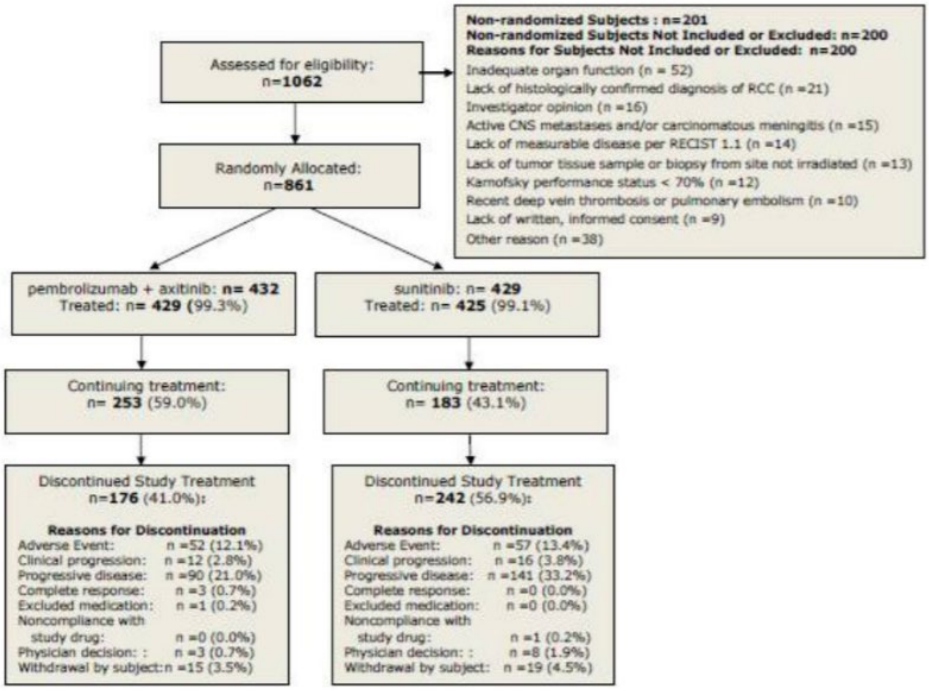
Table 12. Summary of study treatments and subsequent anti-cancer after INV-determined PD on subjects who had VOP request but without IRC verified PD[3]

	Pembrolizumab + axitinib	Sunitinib
Number of subjects without PD verified by IRC at initial VOP request	59	61
Number of subjects received at least one day of study treatment after INV-determined PD	52	31
Median time (range) on study treatment beyond INV-determined PD[1], days	147 (1-420)	28 (2-387)
Number of subjects received any subsequent systemic anti-cancer treatments	21	33
Median time (range) to start 2L systemic anti-cancer treatment after INV-determined PD[2], days	61 (1-295)	45 (4-286)
[1]Duration of study treatment beyond INV-determined PD = last dose date of study treatment minus date of INV-determined PD +1 [2]Time to 2L= first dose date of 2L subsequent therapy minus date of INV-determined PD +1		

c) ***Patient Disposition***

Of the 1062 patients screened (first patient screened on October 6, 2016), 861 were randomly allocated from October 24, 2016 to January 24, 2018 with 432 patients in the pembrolizumab and axitinib arm and 429 patients in the sunitinib arm. The first and last patient visits were October 6, 2018 and August 23, 2018, respectively. There were 429/432 patients (99.3%) that were treated with pembrolizumab and axitinib and 425/429 patients (99.1%) in the sunitinib arm that were treated. In the pembrolizumab and axitinib arm, 253/429 patients (59.0%) continued treatment compared to 183/425 patients (43.1%) in the sunitinib arm.[4]

Figure 3: ***Patient Flow in the KEYNOTE 426 Trial***[4]



d) Limitations/Sources of Bias

- Although KEYNOTE-426 is a randomized trial, due to the open-label study design, the Sponsor, investigator, and participant were aware of the treatment administered. It is possible the trial may be at risk for biases related to blinding that can affect the internal validity. These can include bias in terms of patient selection for eligibility or performance bias because of knowledge of assigned treatment.
- The outcome of duration of response was not powered to detect statistical significance. Therefore, these results should be interpreted with caution.
- While subgroup analyses for the co-primary outcomes of PFS and OS were prespecified,[19] according to the sponsor, no pre-specified interaction test for subgroup analyses were performed. The sponsor noted that no interaction effect between subgroups were expected at study design stage.[3] Thus, the results should be interpreted as exploratory.
- For PRO outcomes, there was no formal hypothesis testing and no multiplicity adjustment was made.[4] The Sponsor noted that patients in the sunitinib group completed the PROs following a 2-week 'off period'.[7] Thus, the PROs assessed in the sunitinib group may not be reflected accurately as treatment with sunitinib was administered over a 6 week treatment cycle and toxicity may have been lowest at the 2 week off period in comparison to the pembrolizumab and axitinib group. Thus, there is potential bias in the PROs obtained in the sunitinib group. For the EQRTC QLQ C30 and FKSI-DRS, the mean change from baseline to week 30 was reported; however, treatment visits were collected up to week 90 where the completion rates were very low.[5] Thus, the longer term impact of treatment on PROs is unclear and the true clinical significance is uncertain.
- The duration of follow-up in the KEYNOTE-426 trial was short. Median OS was not reached in the first interim analysis nor at the updated data cut off January 2, 2019

Long-term OS, PFS, and PROs would confirm the results observed in this study are consistent or maintained over a longer period. Furthermore, long-term safety data will help to capture delayed hepatic adverse events that may occur among patients receiving pembrolizumab treatment over time. Although the protocol-specified criteria for declaring a significant benefit was met for pembrolizumab and axitinib versus sunitinib for PFS and OS and no further alpha-controlled efficacy testing will be performed, as per the trial publication, patients will continue to be followed for assessment of efficacy and safety.[2]

- OS results may be confounded by subsequent treatments that patients received.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

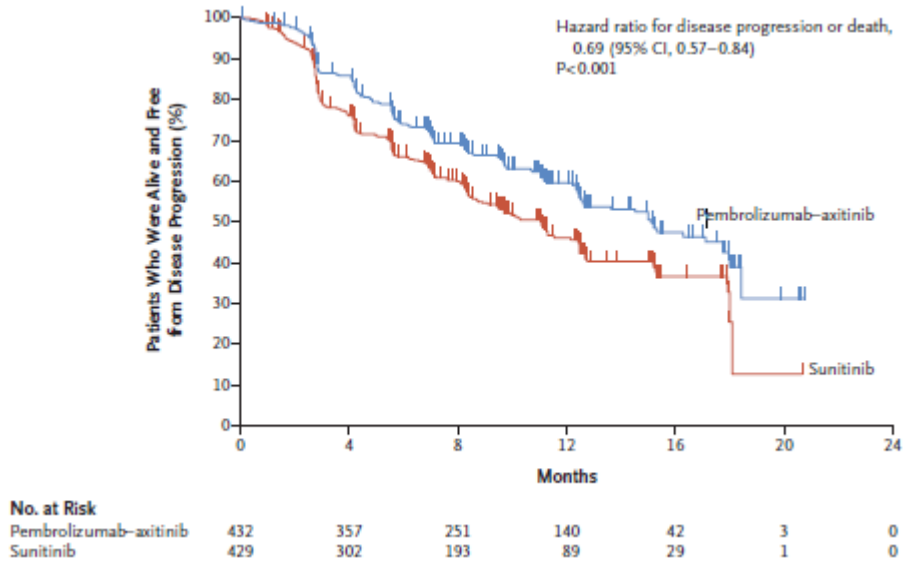
Efficacy Outcomes

All data presented are based on the first interim analysis (data cut off August 24, 2018) unless otherwise specified.

Progression Free Survival -BICR assessed

The median duration of follow up was 13.2 months (range: 0.1-21.5 months) in the pembrolizumab and axitinib group and 12.1 months (range: 0.4-22.0 months) in the sunitinib group. The number of events in the pembrolizumab plus axitinib group was 183 (42.4%) compared to 213 events (49.7%) in the sunitinib group. Progression was documented in 162 patients (37.5%) in the pembrolizumab and axitinib group compared to 184 patients (42.9%)in the sunitinib group. The median progression-free survival improved by 4 months (15.1 months, 95% CI: 12.6-17.7) in the pembrolizumab plus axitinib group and (11.0 months,95% CI: 8.7-12.5) in the sunitinib group. There was a statistically significant improvement for disease progression or death in favour of the pembrolizumab and axitinib group compared to sunitinib group in the ITT population (HR=was 0.69,95% CI: 0.57-0.84, p<0.001).[2] The first interim analysis for PFS was statistically significant and crossed the prespecified boundary of 0.0013.[4] The PFS rate at 12 months was 59.6% (95% CI: 54.3-64.5) in the pembrolizumab and axitinib group compared to 46.1% (95% CI: 40.5-51.5) in the sunitinib group. The PFS rate at 18 months was 41.1% (95% CI: 33.5-48.5) in the pembrolizumab and axitinib group compared to 32.8% (95% CI: 25.4-40.4) in the sunitinib group[4]

Figure 4. Kaplan-Meier curve results for Progression Free Survival[2]



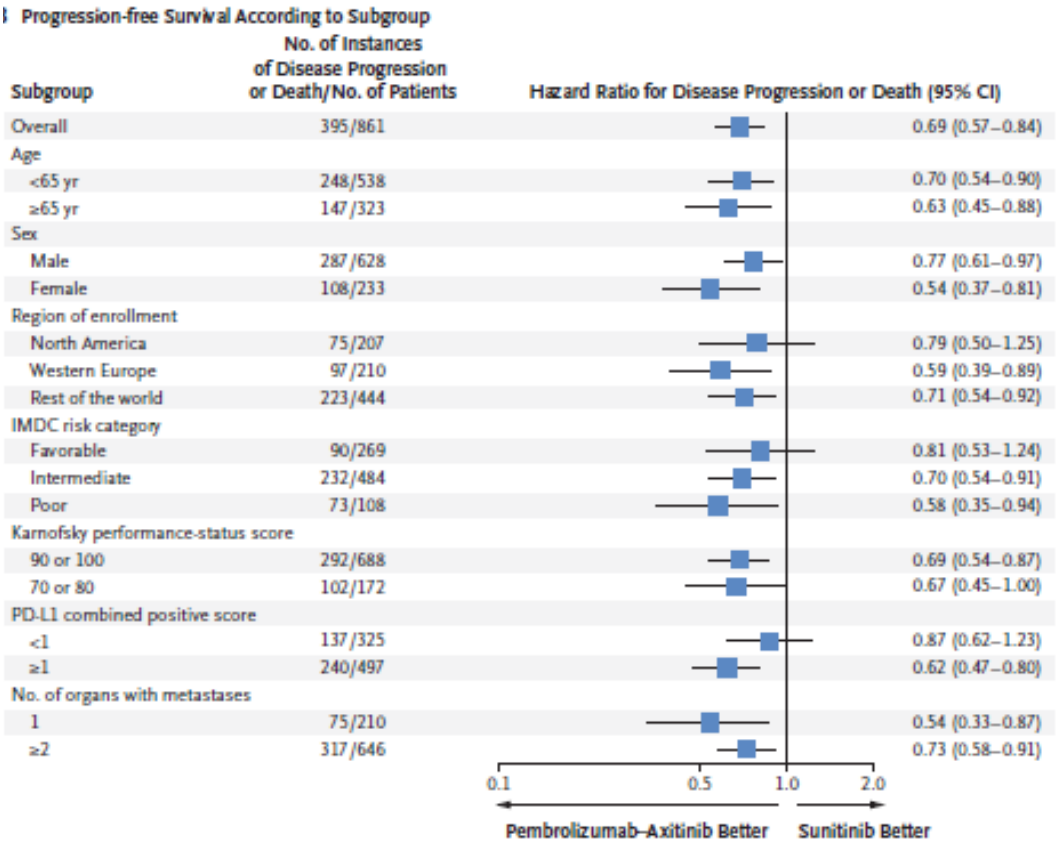
Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Results for PFS based on BICR in the ITT population using the sensitivity censoring rule 1 produced a smaller effect size (HR=0.68, 95% CI: 0.56-0.82, p<0.00005) compared to sensitivity censoring rule 2 (HR=0.65, 95% CI: 0.55-0.78), p <0.00000). [4]

The investigator assessed PFS was not statistically significant (HR=0.82, 95% CI: 0.67-1.00) in the ITT population.[4]

The exploratory subgroup analyses of PFS shown in Table 8 suggests the subgroup analyses of PFS are generally consistent with the overall trial results.

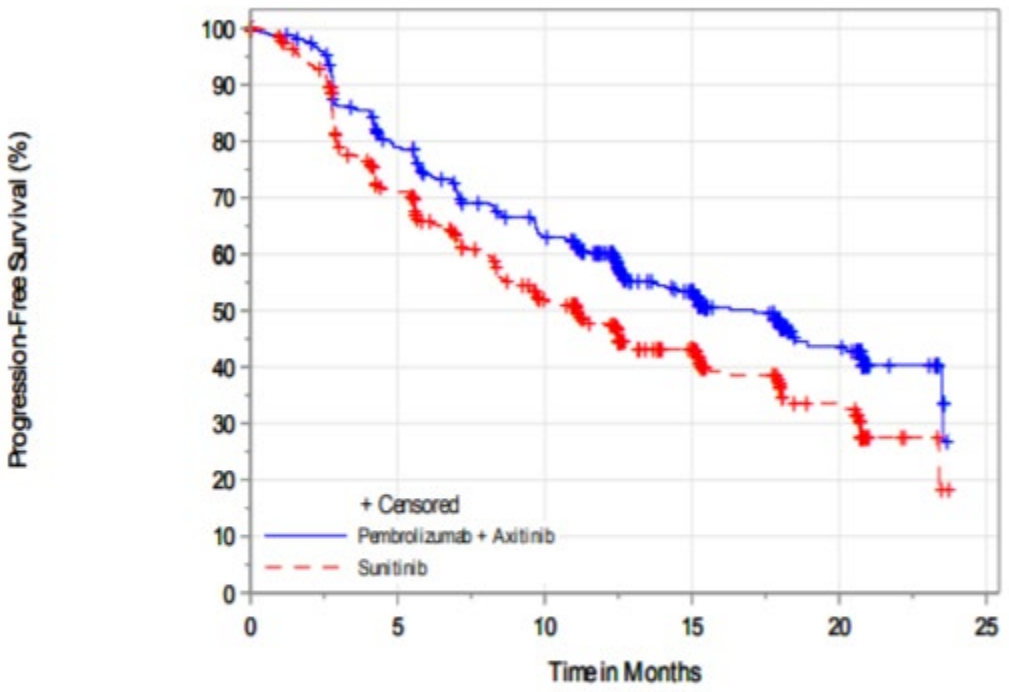
Table 10. Progression Free Survival according to subgroups[2]



Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

At an unplanned data cut-off of January 2, 2019, the median follow-up duration in the ITT population was 17.4 months (range: 0.1-25.6 months) in the pembrolizumab and axitinib group compared to 15.7 months (range: 0.4-26.3 months) in the sunitinib group. [4]The number of events in the pembrolizumab plus axitinib group was 207 (47.9%) compared to 232 events (54.1%) in the sunitinib group. The median PFS improved by 6 months (17.1 months, 95% CI: 13.6-18.9) in the pembrolizumab plus axitinib group and (11.1 months, 95% CI: 8.7-12.5) in the sunitinib group. There was a statistically significant improvement for disease progression or death in favour of the pembrolizumab and axitinib group compared to sunitinib in the ITT population (HR=0.69,95% CI: 0.57- to 0.83) . [4]The PFS rate at 12 months was 60.1% (95% CI: 55.1-64.7) in the pembrolizumab and axitinib group compared to 47.7% (95% CI: 42.5-52.7) in the sunitinib group. [4]

Figure 5. Kaplan-Meier curve for Progression Free Survival (data cut off January 2, 2019)



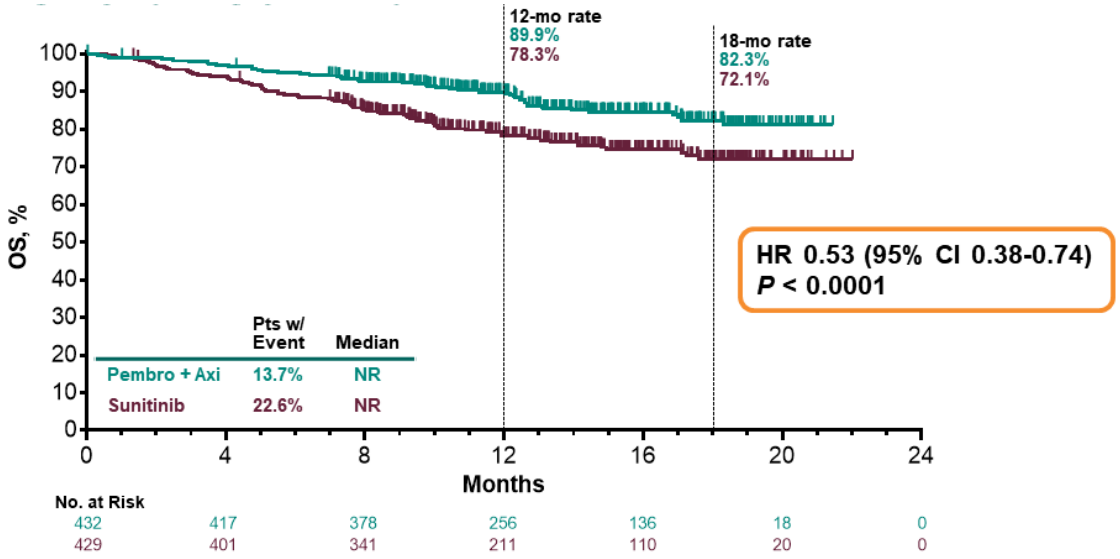
Number of subjects at risk

Pembrolizumab + Axitinib	432	324	247	145	51	0
Sunitinib	429	277	175	90	32	0

Overall Survival-BICR assessed

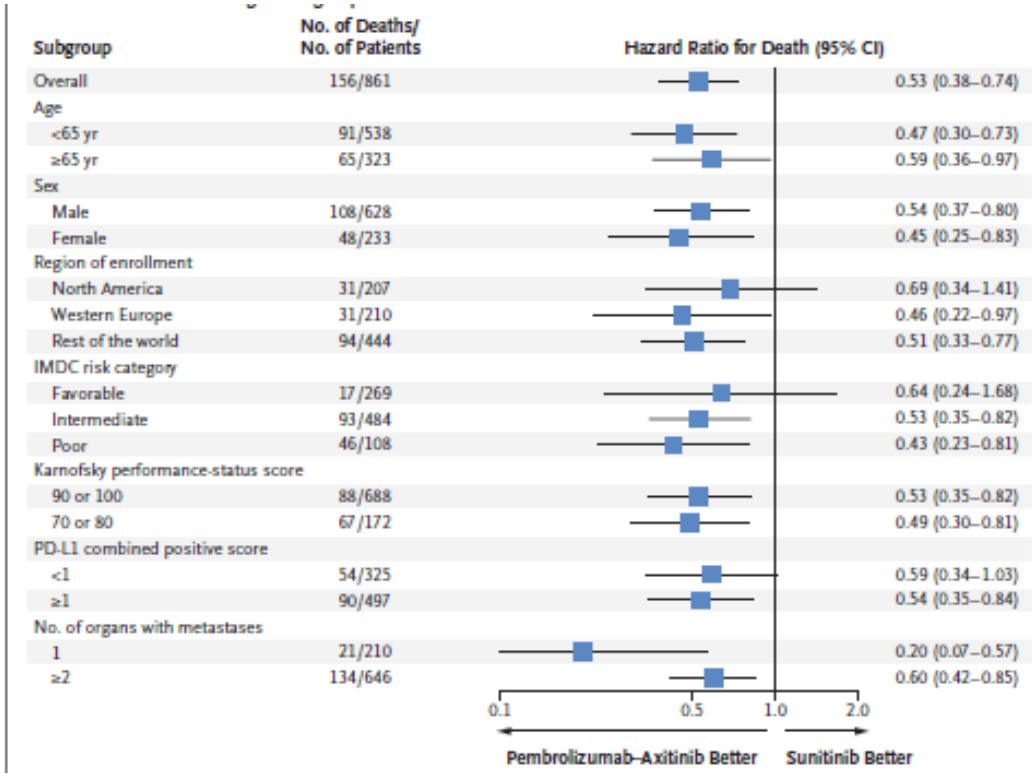
There were 89.9% of patients (95% CI: 86.4-92.4) and 82.3% (95% CI: 77.2–86.3) in the pembrolizumab plus axitinib group alive at 12 months and 18 months, respectively. In the sunitinib group, there were 78.3% of patients (95% CI: 73.8-82.1) and 72.1% of patients (95% CI: 66.3-77.0) alive at 12 months and 18 months respectively.[2] The number of events in the pembrolizumab and axitinib group was 59 (13.7%) compared to 97 events in the sunitinib group (22.6%). [4]The median OS was not reached in either group. There was a statistically significant improvement for OS in the pembrolizumab plus axitinib group versus sunitinib group in the ITT population (HR=0.53,95% CI: 0.38-0.74; P<0.0001).[2] The first interim analysis for OS was statistically significant and crossed the prespecified boundary of 0.0001.[4] Figure 3 presents Kaplan-Meier curve for OS.

Figure 6. Kaplan-Meier curve for Overall Survival[16]



The exploratory subgroup analyses of OS shown in Table 9 suggests these results are consistent with the overall trial results.

Table11. Overall Survival according to baseline characteristics

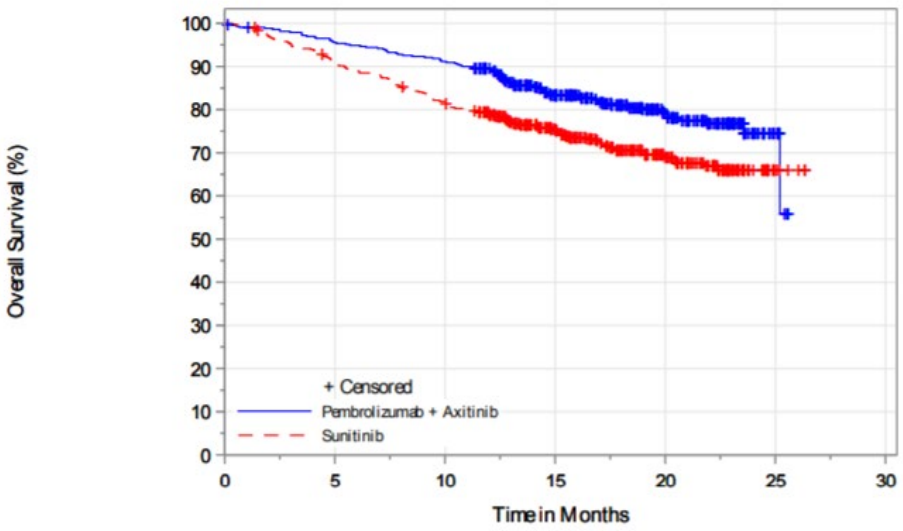


Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

At an unplanned data cut-off of January 2, 2019, the median follow-up duration in the ITT population was 17.4 months (range: 0.1-25.6 months) in the pembrolizumab and axitinib group compared to 15.7 months (range: 0.4-26.3 months) in the sunitinib group. There were 89.5% of patients (95% CI: 86.2-92.1) and 81.0% (95% CI: 76.7–84.6) in the pembrolizumab plus axitinib group alive at 12 months and 18 months, respectively. In the sunitinib group, there were 78.8% of patients (95% CI: 74.7-82.4) and 70.7% of patients (95% CI: 65.8-75.1) alive at 12 months and 18 months, respectively. The number of events in the pembrolizumab and axitinib group was 84 (19.4%) compared to 122 events in the sunitinib group (28.4%). [4] The median OS was not reached in either group. The HR for OS was statistically significant in favour of the pembrolizumab plus axitinib group versus sunitinib group in the ITT population (HR=0.59, 95% CI: 0.45-0.78, P<0.0001). Figure presents Kaplan-Meier curve for overall survival.

The subgroup analyses conducted at the data cut off January 2, 2019 demonstrated consistent results with the August 24, 2018 data cut off.

Figure 7. Kaplan-Meier curve for Overall Survival (ITT population) (data cut off January 2, 2019)[4]



Objective Response Rate-BICR assessment

Since the co-primary endpoints of PFS and OS met the thresholds in the first interim analysis, the key secondary outcome of objective response rate was assessed.

The objective response rate was higher in the pembrolizumab plus axitinib group of 59.3% (95% CI: 54.5-63.9) compared to 35.7% (95% CI: 31.1-40.4) in the sunitinib group 35.7% (95% CI: 31.1-40.4). [2]A complete response was reported in 25 patients (5.8%) in the pembrolizumab plus axitinib group and 8 patients (1.9%) in the sunitinib group. Partial response was observed in 231 patients (53.5%) in the pembrolizumab plus axitinib group versus 145 patients (33.8%) in the sunitinib group. Stable disease was reported in 106 patients (24.5%) compared to 169 patients (39.4%). [2]Table 11 displays a summary of confirmed objective response.

Table 12. Summary of Confirmed Response [2]

Variable	Pembrolizumab–Axitinib (N = 432)	Sunitinib (N = 429)
Objective response rate — % (95% CI)†	59.3 (54.5 to 63.9)	35.7 (31.1 to 40.4)
Best overall response — no. (%)		
Complete response	25 (5.8)	8 (1.9)
Partial response	231 (53.5)	145 (33.8)
Stable disease	106 (24.5)	169 (39.4)
Progressive disease	47 (10.9)	73 (17.0)
Could not be evaluated‡	8 (1.9)	6 (1.4)
Not assessed§	15 (3.5)	28 (6.5)
Median time to response (range) — mo¶	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
Median duration of response (range) — mo‖	Not reached (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

* Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by means of blinded, independent central review of radiologic imaging. Percentages may not total 100 because of rounding.
† The estimated treatment difference in objective response between the pembrolizumab–axitinib group and the sunitinib group was 23.6 percentage points (95% CI, 17.2 to 29.9; P<0.001) and was calculated with the use of the method of Miettinen and Nurminen and stratified according to IMDC risk group[14] (favorable, intermediate, or poor) and geographic region (North America, Western Europe, or the rest of the world).
‡ The patients who could not be evaluated included those who had one or more postbaseline imaging assessments, none of which could be evaluated for response according to RECIST, version 1.1.
§ The patients who were not assessed included those who did not have any postbaseline imaging assessments.
¶ The median time to response was calculated only for patients who had a complete or partial response (256 patients in the pembrolizumab–axitinib group and 153 patients in the sunitinib group).
‖ The median duration of response was calculated with the use of the Kaplan–Meier method with data from patients who had a complete or partial response (256 patients in the pembrolizumab–axitinib group and 153 patients in the sunitinib group). Plus signs in the ranges indicate responses that were ongoing at the time of data cutoff.

Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

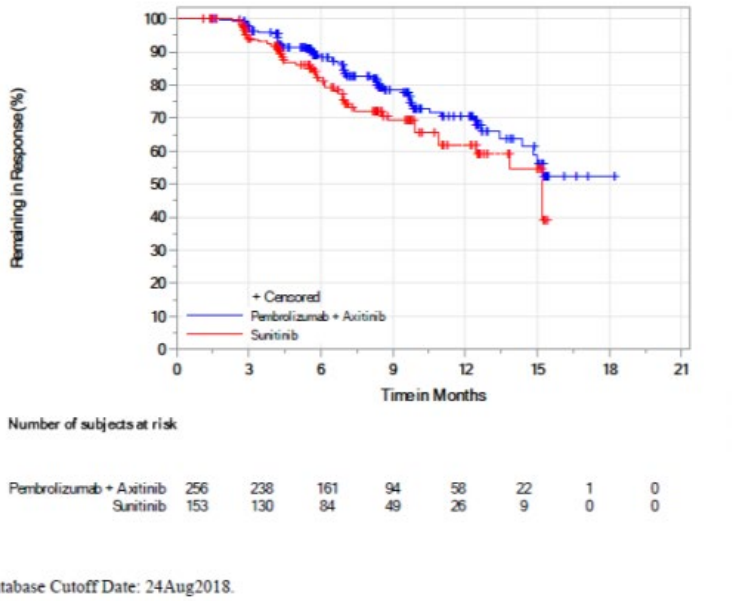
At the updated data cut off of January 2, 2019 in the ITT population, the objective response rate in the pembrolizumab plus axitinib group was 60.0% (95% CI: 55.2-64.6) compared to 38.5% (95% CI: 33.8-43.2) in the sunitinib group with a statistically significant difference of 21.5% (95% CI: 15.1-27.8; p<0.0001). [4]

Duration of Response-BICR assessed

The median duration of response was not reached in the pembrolizumab plus axitinib group (range: 1.4+ to 18.2+ months), and the median duration of response was 15.2 months (range: 1.1+ to 15.4+) in the sunitinib group. The plus signs denotes an ongoing response at the time of data cut off.[2] The median time to response was 2.8 months (range:

1.5-16.6) in the pembrolizumab and axitinib group compared to 2.9 months (range: 2.1-15.1) in the sunitinib group.[2] Approximately 70.6% of patients reported an ongoing response at 1 year in the pembrolizumab plus axitinib group and 61.6% in the sunitinib group. [2]

Figure 8. Kaplan-Meier curve for Duration of Response (ITT population)[4]



The investigator assessed DOR was met in the pembrolizumab and axitinib arm 18.0 months (1.3+ to 18.2+) and consistent with the BICR assessed DOR in the sunitinib arm.

Patient reported outcomes

On Day 1 of each cycle, PROs were assessed in the pembrolizumab and axitinib group whereas PROs were assessed on Days 1 and 29 of each cycle until cycle 4 then Day 1 of each subsequent cycle following the 2 week off treatment period.[4] The protocol specified that ePROs were administered to randomized patients prior to drug administration, adverse event evaluation, and disease status notification. If the PROs were not completed by a patient, the reason for non completion was documented. A window of +/-7 days was provided to conduct PRO visit assessments.[2]

At baseline, the number of patients that completed the FKSI-DRS was 399 (93.2%) in the pembrolizumab and axitinib group compared to 409 patients (97.1%) in the sunitinb group. Compliance was defined as the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design (i.e., adverse event, death, discontinuation, translations not available, and no visit scheduled).[5] Data on compliance was reported up to week 90.[5] Pembrolizumab-axitinib did not result in meaningful changes in the FKSI-DRS compared with sunitinib.[7] The median time to true deterioration was not reached in either treatment group.[4] There was no statistically

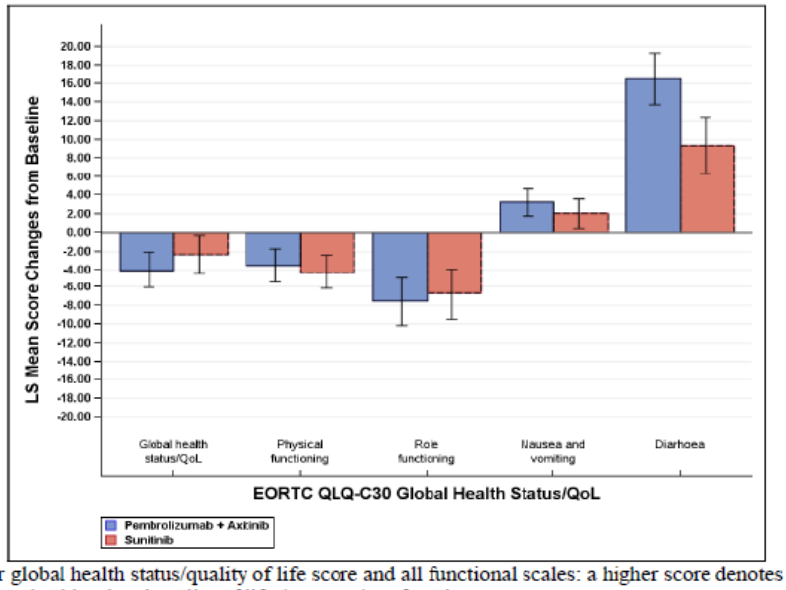
significant difference in the time to true deterioration assessed by the FKSI-DRS (i.e., time to first onset of 3 or more decrease from baseline with confirmation under right-censoring rule) between the pembrolizumab and axitinib group and sunitinib group (HR 1.44, 95% CI: 1.14-1.82; nominal p=0.999).[4]

At baseline, the number of patients that completed the EORTC QLQ-C30 was 395 (92.3%) in the pembrolizumab and axitinib group compared to 409 patients (96.9%) in the sunitinib group. The definition of compliance was the same in the FKSI-DRS and the EORTC QLQ-C30. Compliance was reported up to week 90.[5] Based on the supplemental Statistical Analysis Plan (sSAP)[19], the sponsor noted that the primary analysis time point for PRO analyses was Week 54 based on the median PFS for the sunitinib arm. However, this was dependent on at least 60% completion and 80% compliance based on combined groups prior to unblinding at the primary time point. To avoid unstable estimates with excessive missing data (i.e., completion <60%, compliance <80%), the sSAP outlined that the next earliest timepoint was used. Thus, week 30 was the primary time point where completion and compliance was 60% and 80% respectively.[6] .At week 30 the compliance was 85.9% and 88.9% for the EORTC QLQ-C30 questionnaire in the pembrolizumab in combination with axitinib group and sunitinib group, respectively. The change from baseline to week 30 based on the least square mean calculated between the pembrolizumab plus axitinib group and the sunitinib group was not statistically significant -1.70 (95% CI: -4.34-0.94), p=0.207.[7]

There were no clinically meaningful difference from baseline to Week 30 in the EORTC QLQ-C30 global health status/QoL score in both study groups.[4]

From baseline to week 30, for the EORTC QLQ-C30 functional scales (i.e., physical functioning and role functioning) and the symptom scales (i.e., nausea and vomiting), there was no statistically significant difference between the pembrolizumab plus axitinib group compared to sunitinib. However, for the symptom scale of diarrhea, from baseline to week 30, worsening symptoms of diarrhea was observed in the pembrolizumab plus axitinib group compared to sunitinib. The sponsor conducted an exploratory adjustment for treatment exposure which resulted in a similar event rate of diarrhea between the pembrolizumab plus axitinib group and sunitinib group. [6] Results are shown in figure 9.

Figure 9. Change from Baseline for EORTC QLQ-C30 Global Health Status/QoL and Selected functional and symptom scales at week 30 [4,8]



For global health status/quality of life score and all functional scales: a higher score denotes better health related quality of life (HRQOL) or function.
For symptoms scales: a higher score denotes worse symptoms.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adplda]

Safety Outcomes

In the first interim analysis (data cut off date August 24, 2018), safety was assessed in the as-treated population defined as all patients who were randomly assigned that received one or more doses of trial treatment. Among the 429 patients that received pembrolizumab plus axitinib, 98.4% experienced an adverse event of any cause compared to 99.5% of the 425 patients who received sunitinib experienced adverse events of any cause. [2]

Grade 3 or higher AEs were slightly higher in 75.8% of patients in the pembrolizumab plus axitinib group compared to 70.6% of patients in the sunitinib group. Grade 3 or higher events that were attributed to trial treatment as judged by the investigator were reported in 62.9% of patients in the pembrolizumab plus axitinib group compared to 58.1% of patients in the sunitinib group.[2]Hypertension was the most common Grade 3 or higher AE that occurred in pembrolizumab plus axitinib (21.2%) and sunitinib (18.4%) followed by diarrhea in the pembrolizumab plus axitinib group (7.2%) versus sunitinib group (4.5%).

In the pembrolizumab and axitinib group, discontinuation of either drug due to adverse events of any cause occurred in 30.5% of patients, discontinuation of both pembrolizumab and axitinib in 10.7% of patients, interruption of either drug in 69.9% of patients, and dose reduction of axitinib in 20.3%. The median time to discontinuation of pembrolizumab due to drug-related adverse events was 65 days and 63 days for both drugs.[4] In the sunitinib group, discontinuation of either drug due to adverse events of any cause occurred in 13.9% of patients, interruption of sunitinib in 49.9% of patients, and dose reduction of sunitinib in 30.1%.[2]

Discontinuation due to drug-related SAEs occurred in 17% of patients in the pembrolizumab and axitinib group compared to 9.9% of patients in the sunitinib group. Four patients (0.9%) in the pembrolizumab and axitinib group died from adverse events attributed to study treatment by the investigator (i.e. one patient each of myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis). There were seven patients (1.6%) in the sunitinib group whom died from adverse events attributed to study treatment by the investigator (i.e. one patient each of acute myocardial infarction, cardiac arrest, gastrointestinal hemorrhage, intracranial hemorrhage, hepatitis fulminant, malignant neoplasm progression, and pneumonia).[2] No deaths related to study drug were reported. Table 13 outlines the adverse events attributed to study treatment by the investigator.

Table 13. Adverse Events Attributed to Study Treatment by the Investigator That Occurred in 10% of More of Patients in the As-Treated Population[2]

Event	Pembrolizumab-Axitinib (N=429)		Sunitinib (N=425)	
	number of patients (percent)			
Any event	413 (96.3)		415 (97.6)	
Grade 3, 4, or 5	270 (62.9)		247 (58.1)	
Led to discontinuation of any treatment	111 (25.9)		43 (10.1)	
Led to discontinuation of both pembrolizumab and axitinib	35 (8.2)		—	
Led to axitinib or sunitinib dose reduction	86 (20.0)		121 (28.5)	
Led to interruption of any treatment	267 (62.2)		171 (40.2)	
Led to death	4 (0.9)†		7 (1.6)‡	
	Any Grade	Grade 3, 4, or 5†	Any Grade	Grade 3, 4, or 5‡
Diarrhea	210 (49.0)	31 (7.2)	175 (41.2)	19 (4.5)
Hypertension	179 (41.7)	91 (21.2)	184 (43.3)	78 (18.4)
Hypothyroidism	135 (31.5)	1 (0.2)	119 (28.0)	0
Fatigue	130 (30.3)	10 (2.3)	142 (33.4)	21 (4.9)
Palmar-plantar erythrodysesthesia	119 (27.7)	22 (5.1)	168 (39.5)	15 (3.5)
Alanine aminotransferase increased	102 (23.8)	52 (12.1)	54 (12.7)	11 (2.6)
Dysphonia	98 (22.8)	1 (0.2)	12 (2.8)	0
Aspartate aminotransferase increased	97 (22.6)	29 (6.8)	59 (13.9)	7 (1.6)
Decreased appetite	94 (21.9)	9 (2.1)	106 (24.9)	2 (0.5)
Nausea	91 (21.2)	2 (0.5)	111 (26.1)	4 (0.9)
Proteinuria	66 (15.4)	11 (2.6)	39 (9.2)	6 (1.4)
Stomatitis	61 (14.2)	3 (0.7)	86 (20.2)	9 (2.1)
Mucosal inflammation	55 (12.8)	4 (0.9)	90 (21.2)	7 (1.6)
Pruritus	53 (12.4)	1 (0.2)	18 (4.2)	0
Arthralgia	52 (12.1)	3 (0.7)	15 (3.5)	2 (0.5)
Hyperthyroidism	52 (12.1)	4 (0.9)	14 (3.3)	0

Asthenia	50 (11.7)	6 (1.4)	54 (12.7)	12 (2.8)
Rash	46 (10.7)	1 (0.2)	38 (8.9)	1 (0.2)
Dysgeusia	40 (9.3)	1 (0.2)	129 (30.4)	0
Vomiting	34 (7.9)	1 (0.2)	56 (13.2)	3 (0.7)
Platelet count decreased	14 (3.3)	1 (0.2)	76 (17.9)	31 (7.3)
Anemia	12 (2.8)	1 (0.2)	69 (16.2)	13 (3.1)
Dyspepsia	12 (2.8)	0	48 (11.3)	1 (0.2)
Thrombocytopenia	8 (1.9)	0	94 (22.1)	22 (5.2)
Neutropenia	6 (1.4)	1 (0.2)	79 (18.6)	28 (6.6)
Neutrophil count decreased	3 (0.7)	1 (0.2)	48 (11.3)	29 (6.8)

* Listed are all adverse events that occurred during randomly allocated study treatment or within the 30 days thereafter (within 90 days for serious events) and were attributed to study treatment by the investigator. The as-treated population included all patients who underwent randomization and received ≥1 dose of study treatment. Events are listed in descending order of frequency in the pembrolizumab-axitinib group.

† Four (0.9%) patients in the pembrolizumab-axitinib group died from adverse events attributed to study treatment by the investigator: one patient each of myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis.

‡ Seven (1.6%) patients in the sunitinib group died from adverse events attributed to study treatment by the investigator: one patient each of acute myocardial infarction, cardiac arrest, gastrointestinal hemorrhage, hemorrhage intracranial, hepatitis fulminant, malignant neoplasm progression, and pneumonia.

Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380,

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There were 51.3% of patients in the pembrolizumab plus axitinib group that experienced any grade adverse event of interest compared to 36.2% of patients in the sunitinib group. Adverse events of interest were identified using a list of terms specified by the sponsor and were assessed irrespective of whether the investigator determined that they were related to treatment.[2] The most commonly reported Grade 3,4 or 5 AEs with possible immune-mediated cause and infusion reactions were hypothyroidism that occurred in 1 patient (0.2%) in the pembrolizumab plus axitinib group and sunitinib group followed by hyperthyroidism which occurred in 5 patients (1.2%) in the pembrolizumab plus axitinib group and 0 patients in the sunitinib group. Results are presented in Table 14.

Table 14. Adverse Events of Interest in the As-treated population[2]

Event	Pembrolizumab-Axitinib (N=429)		Sunitinib (N=425)	
	Any Grade	Grade 3, 4, or 5†	Any Grade	Grade 3, 4, or 5‡
	number of patients (percent)			
Any event	220 (51.3)	46 (10.7)	154 (36.2)	8 (1.9)
Hypothyroidism	152 (35.4)	1 (0.2)	134 (31.5)	1 (0.2)
Hyperthyroidism	55 (12.8)	5 (1.2)	16 (3.8)	0
Adrenal insufficiency	13 (3.0)	3 (0.7)	1 (0.2)	0
Hepatitis	12 (2.8)	10 (2.3)	2 (0.5)	1 (0.2)
Pneumonitis	12 (2.8)	2 (0.5)	1 (0.2)	0
Thyroiditis	12 (2.8)	1 (0.2)	2 (0.5)	0
Colitis	11 (2.6)	8 (1.9)	3 (0.7)	0
Severe skin reactions	8 (1.9)	5 (1.2)	6 (1.4)	3 (0.7)
Infusion reactions	7 (1.6)	1 (0.2)	4 (0.9)§	1 (0.2)§
Nephritis	6 (1.4)	1 (0.2)	1 (0.2)	0
Hypophysitis	5 (1.2)	4 (0.9)	0	0
Myasthenic syndrome	4 (0.9)	2 (0.5)	0	0
Myositis	4 (0.9)	1 (0.2)	0	0
Myocarditis	2 (0.5)	2 (0.5)	0	0
Pancreatitis	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Uveitis	2 (0.5)	0	0	0
Type 1 diabetes mellitus	1 (0.2)	1 (0.2)	0	0

* Listed are adverse events with a possible immune-mediated cause and infusion reactions that occurred during study treatment or within the 90 days thereafter, regardless of attribution to study treatment or immune relatedness by the investigator. The specific events are based on a list of terms specified by the sponsor. In addition to the specific terms listed, related terms were also included. The as-treated population included all patients who underwent randomization and received ≥1 dose of study treatment. Events are listed in descending order of frequency in the pembrolizumab-axitinib group.

† Three (0.7%) patients in the pembrolizumab-axitinib group died from adverse events of interest: one patient each with myasthenic syndrome (recorded as myasthenia gravis), myocarditis, and pneumonitis.

‡ One (0.2%) patient in the sunitinib group died from an adverse event of interest: hepatitis (recorded as hepatitis fulminant).

§ The adverse event of interest termed "infusion reactions" includes the preferred terms anaphylactic reaction and hypersensitivity, which explains why patients in the sunitinib group are indicated as having an "infusion reaction."

Source: From the New England Journal of Medicine. Rini, B.I., Plimack, E.R., Stus, V. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, volume 380, page no: 1116-1127. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

In the as-treated population, the proportion of patients that experienced a dose change from initial dose were similar in the pembrolizumab and axitinib group compared to sunitinib group. There were 69 patients (16.1%) who experienced dose escalation from initial dose in the pembrolizumab and axitinib group compared to 284 patients (66.2%) that had a dose reduction from initial dose. In the axitinib group, no patients had dose escalation from initial dose where as 207 patients (48.7%) had a dose reduction from initial dose.[4]

At the updated data cut off of January 2, 2019, 65 patients (15.2%) in the pembrolizumab and axitinib arm and 61 patients (14.4%) in the sunitinib arm had discontinued study treatment(s) due to adverse events . There were 41 patients in the pembrolizumab and

axitinib group who discontinued study treatment due to adverse events and received no further anti-cancer treatments. Of these 41 patients, 24 were alive and 17 died. In the sunitinib group, 31 patients discontinued study treatment due to an adverse event and received no additional anti-cancer therapy. Of these 31 patients, 13 patients were alive and 18 patients died. [4]

6.4 Ongoing Trials

There are no ongoing trials.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma.

- Summary of sponsor-submitted network meta-analysis comparing pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma[17]

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary of sponsor-submitted network meta-analysis comparing pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma

7.1.1 Objective

To summarize and critically appraise the methods and findings of the sponsor-submitted network meta-analysis (NMA) comparing pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma (mRCC).

7.1.2 Findings

Methods

Systematic Review

The sponsor provided a network meta-analysis (NMA) based on a systematic literature review (SLR) to identify mRCC trials including all lines of treatment and all histologies (Table 1 for inclusion/exclusion criteria). The following databases were searched through the Ovid platform to identify relevant randomized controlled trials (RCTs) or pooled analyses of RCTs (phase II and phase III): MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials. Study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) for MEDLINE and EMBASE were used to identify clinical trials (http://www.sign.ac.uk/methodology/search-filters.html). The population terms were adapted from MeSH terms. The intervention terms included terms related to the generic and brand name of the interventions of interest. Searches were supplemented from the US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) and the European Union (EU) Clinical Trials Register (clinicaltrialsregister.eu) to identify completed clinical trials not yet published that met inclusion criteria with results available, as well as the most recent two years of selected conferences.

Abstracts were screened, followed by full-text article screening of potentially relevant references. Data was extracted from relevant full-text studies into a Microsoft Excel workbook. The quality of individual RCTs was assessed using the quality assessment instrument endorsed by the National Institute for Health Care and Excellence in the UK (NICE) in the Single Technology Appraisal Company Evidence Submission User Guide. Screening, data extraction and quality appraisal were all done by two independent researchers. Following reconciliation, a third reviewer was included to reach consensus on any remaining discrepancies.

Table 1: Study selection criteria to identify trials for the systematic literature review

Criteria	Description
Population(s)	**Inclusion criteria:** **A. Metastatic Renal Cell Carcinoma (clear cell histology)** Adults diagnosed with histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features with the following staging: • locally advanced (T3a–T4 per American Joint Committee on Cancer [AJCC]) • metastatic (Stage IV per AJCC), or • chemo-naïve or -experienced relapsed/recurrent disease of earlier AJCC stage **B. Metastatic Renal Cell Carcinoma (non-clear cell histology)** Adults diagnosed with histologically confirmed diagnosis of RCC with non-clear cell component with or without sarcomatoid features with the following staging: • locally advanced (T3a–T4) • metastatic (Stage IV), or • chemo-naïve relapsed/recurrent disease of earlier AJCC stage **Exclusion criteria:** RCC patients with clear cell histology who have experienced prior systemic therapy
Interventions	**Clear cell cohort** • 1L Therapy – any of the following as monotherapy or combination therapy o Pembrolizumab+axitinib o Sunitinib o Pazopanib o Axitinib o Sorafenib o Bevacizumab+interferon (IFN) o IFN o Ipilimumab + nivolumab o Temsirolimus o Atezolizumab+bevacizumab o Avelumab+axitinib o Pembrolizumab+epacadostat o Cabozantinib o Nivolumab o High-dose interleukin-2 (IL-2) o Tivozanib o Crizotinib o Volitinib o Ascorbic Acid o • 2L+ therapy – any of the following as monotherapy or combination therapy: o Pembrolizumab+axitinib o Cabozantinib o Everolimus o Nivolumab o Axitinib o Lenvatinib o Ipilimumab o Pazopanib o Sunitinib o Bevacizumab o Sorafenib o High-dose IL-2 o Lenvatinib + everolimus o Temsirolimus o IFN o Tivozanib o CB-839 o CM082 o TRC105 o Anti-OX40 Antibody PF-04518600 o MLN0128+MLN1117 o Crizotinib o Volitinib **Non-clear cell cohort** • 1L therapy – any of the following as monotherapy or combination therapy: o Pembrolizumab+axitinib o Sunitinib o Axitinib o Bevacizumab o Cabozantinib o Erlotinib o Everolimus o Lenvatinib+everolimus o Nivolumab o Pazopanib o Sorafenib o Temsirolimus o IFN o Crizotinib o Volitinib
Comparisons	At least one of the following: • Any intervention of interest • Placebo
Outcomes	At least one of the following outcomes: • Overall survival (OS) • Progression-free survival (PFS) • Duration of response (DOR) • Time to progression (TTP) • Overall/objective response rate (ORR) • Complete response (CR) • Partial response (PR) • Stable disease (SD) • Progressive disease (PD) • Disease control rate (DCR) • Any adverse event (AE) • Any Grade 3-5 AE • Discontinuation due to AE • Treatment-emergent adverse events • Study withdrawals • Patient reported outcomes (PRO) (e.g. EQ-5D, EORTC QLQ-C30)
Study design	Inclusion criteria: • RCTs o Parallel group o Cross-over o Post-hoc subgroup analyses and open-label extension studies • Pooled analyses of RCTs (phase II and phase III) Exclusion criteria: • Non-randomized controlled trials • Single-arm trials • Prospective and retrospective cohort studies • Case-control studies • Cross-sectional studies Case reports and case series

Feasibility Assessment

A feasibility assessment was conducted to determine the appropriateness of an NMA, which included: 1) determination of whether the RCT evidence for the interventions of interest formed one evidence network for each population and outcome of interest; and 2) assessment of the

distribution of treatment, outcomes, study and patient characteristics that may affect treatment effects across direct comparisons of the evidence networks. The report stated that the most important treatment-effect modifiers identified were risk score (assessed by International Metastatic Renal Cell Carcinoma Database or Memorial Sloan-Kettering Cancer Center scoring), programmed death-ligand 1 (PD-L1) status, age, and performance score (Eastern Cooperate Oncology Group (ECOG) or Karnofsky performance score (KPS)).

Network Meta-Analysis

The analyses were conducted using a Bayesian framework.[20] Prior to conducting this NMA, the consistency between direct and indirect comparisons was evaluated for networks that included closed loops. A synthesis of only direct evidence was performed using independent-means models where pooled estimates for all the different direct comparisons were obtained simultaneously. Additionally, relative treatment effects for all the possible comparisons in the network based on indirect evidence only were assessed with 'edge-splitting', whereby the NMA is repeatedly conducted with the direct evidence removed from the dataset in each analysis.

RCTs identified in the SLR that formed part of one evidence network and were deemed sufficiently similar for each population of interest were synthesized in the NMA by outcome of interest to contrast the relative treatment effect. While both fixed and random-effects models were considered, it was stated that insufficient trials were available to achieve stable estimates of between-study heterogeneity, and therefore only the fixed-effects results were presented.

Binary outcomes (such as overall response rate (ORR) and discontinuations due to adverse events (AE)) were analyzed in the NMA based on the proportion of patients experiencing the event of interest, using a regression model with a binomial likelihood and logit link. Normal non-informative prior distributions were used with a mean of 0 and a variance of 10 000, and relative treatment effects were expressed as odds ratios (OR). The posterior distributions of relative treatment effects were summarized by the median and 95% credible intervals (CrIs), which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions.

Time to event outcomes (overall survival (OS) and progression-free survival (PFS)) were modeled using three methodologies due to the potential for the violation of the proportional hazards assumption: 1) constant hazard ratios (HR) (which assumes proportional hazards between treatment)s; 2) time-varying HRs (which does not assume proportional hazards between treatments) relative to sunitinib as the comparator; 3) Kaplan-Meier curve synthesis. There were several limitations to these approaches, which are further discussed in the Critical Appraisal section.

For the first approach (constant HRs) which assumed proportional hazards, a regression model was performed with a contrast-based normal likelihood for the log HR and corresponding standard error (SE) of each trial or comparison in the network. Normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

Methods for analysis of survival data that do not assume a constant hazard were based on those proposed by Ouwens et al and Jansen.[21-23] This approach models a multidimensional treatment effect as using known parametric survival functions or fractional polynomials, and the difference in the parameters were considered the multidimensional treatment effect, which were synthesized (and indirectly compared) across studies. The treatment effects were represented by multiple parameters rather than a single parameter. Competing survival distributions were considered using the multivariate NMA framework for OS and PFS. The following distributions were used: Weibull, Gompertz, and second order fractional polynomials including p1=0 or 1 and p2= -1, 0.5, 0, 0.5, or 1. For the relative treatment effects in the 2nd order fractional polynomial framework, models were assessed which assumed: 1) treatment only had an impact on two of the three parameters describing the hazard function over time (i.e. one scale and one

shape parameter), and 2) treatment had an impact on all three parameters describing the hazard function over time (i.e. one scale and two shape parameters).

For each treatment arm of each study in the NMA, the reported Kaplan-Meier (KM) curves were digitized using DigitizeIt; http://www.digitizeit.de. The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models. A Markov Chains Monte Carlo (MCMC) method was used to estimate the parameters of the different models in OpenBUGS software package in R version 3.0.3. A first series of iterations from the OpenBUGS sampler were used as a burn-in, and the iterations based on additional iterations using two chains.

Results were presented with estimates for treatment effects of each intervention relative to the reference treatment (sunitinib). The posterior distributions of relative treatment effects were summarized by the median and 95% credible intervals (CrIs) which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions. Cross tables with relative treatment effect estimates between all interventions of interest along with the 95% CrIs for all outcomes were presented, except for time-to-event outcomes based on Kaplan Meier outcomes. Results for binary outcomes were presented as ORs. Results of time-to-event outcomes based on reported HRs were also presented as HRs, and results of time-to-event outcomes based on KM curves were presented in terms of HRs up until 20 months. The report stated that this cut-off was based on the maximum follow-up time of KEYNOTE 426 found in in the PFS KM curve for the intention-to-treat (ITT) population, which was 21 months. In order to void sensitivity in tail ends of fractional polynomials model results due to censoring, the time varying HR analyses were run up until 20 months. The same cut-off was used for OS to maintain consistency, even though the maximum follow-up time was longer for OS than PFS.

The report stated that subgroup analyses were constructed for characteristics identified in the feasibility assessment that were considered potential effect modifiers in the treatment of mRCC. These subgroups included: favorable risk, intermediate risk, poor risk, intermediate and poor risk, PD-L1+, PD-L1-, age ≥65 years, age <65 years, KPS score 70-80, and KPS score 90-100, however the report noted that subgroup analyses included smaller sample sizes compared to the base case. Connected networks for PFS were available for the following subgroups: intermediate and poor risk, favorable risk, intermediate risk, poor risk, PD-L1+, PD-L1-, age 65 years and older, age younger than 65 years, KPS score 70/80, and KPS score 90/100. Connected networks for OS were available for the following subgroups: intermediate and poor risk, favorable risk, intermediate risk, poor risk, and PD-L1+. Subgroup networks were not available for ORR or safety outcomes. The networks relevant to the Canadian settings (eg. 'intermediate and poor risk' and 'favourable risk', which evaluated risk based on the IMDC criteria) are discussed below.

[24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

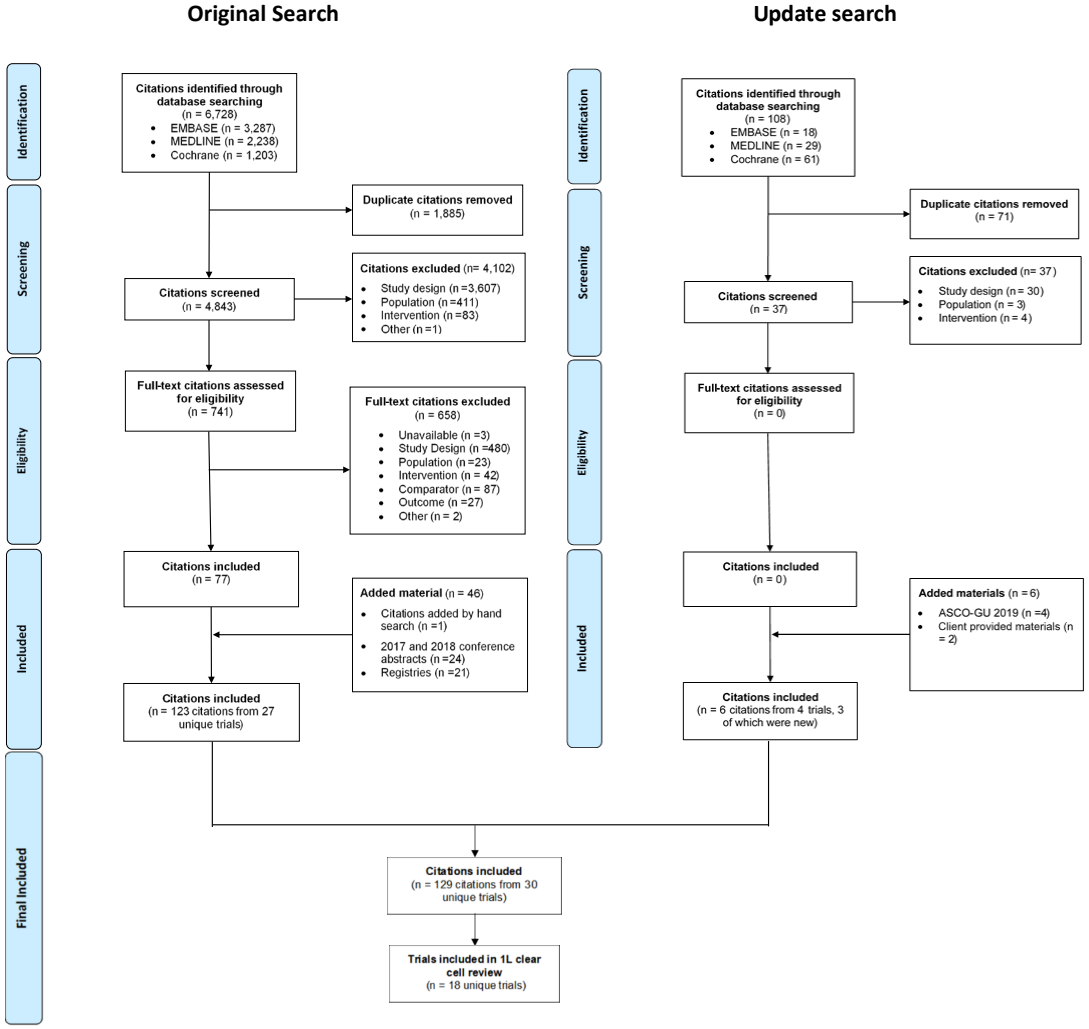
Results

Networks

The SLR identified 129 citations from 30 unique trials, of which 18 unique trials were included in the feasibility assessment of the NMA for 1L clear cell population (non clear cell populations were not included in this NMA) (Figure 1). The base case analysis included trials conducted

among naïve advanced metastatic ccRCC participants and trials that reported outcomes for this population as a subgroup of a larger trial. Trials restricted to intermediate and poor risk participants were excluded from the base case analyses but were considered for inclusion in subgroup analyses.

Figure 1. Study selection flow diagram



All trials included populations >18 years of age. The included trials contained both Phase 2 and 3 trials, and there was a mix of open-label and double-blind masking, and single centre and multi-centre trials. Baseline characteristics of the patients, prior treatments and metastatic sites were missing in many of the trials. In trials reporting on these patient characteristics, 0-62% had an ECOG of 0, 24-59% had an ECOG of 1, 1-76% had an ECOG of 2, 21-55% had a favourable MSKCC, 24-69% had an intermediate MSKCC and 0-76% had a poor MSKCC. In the trials reporting the prior treatment and metastatic sites for patients, 41-100% had prior nephrectomy, 7.6-22.7% had prior radiation, 59-86.6% had lung metastases, 15-37% had bones metastases, 6-27% had liver metastases, and 34-70% had lymph node metastases. Further patient and treatment characteristics are reported in Table 2.

Table 2. Characteristics of RCTs included in the feasibility assessment

Trial ID	Treatment	N	Median age (range)	Agent 1	Agent 2
ARCC	Interferon alfa	207	60 (23-86)	Interferon alfa. SC 9 million units, three times weekly	--
	Temsirolimus	209	58 (32-81)	Temsirolimus, IV 25mg, once weekly UDP	--
	Temsirolimus + interferon alfa	210	59 (32-82)	Temsirolimus, IV 15mg, once weekly UDP	Interferon alfa. SC 6 million units, three times weekly
AVOREN	Bevacizumab + interferon	327	61 (30-82)	Bevacizumab, IV 10mg/kg, every two weeks UDP	Interferon, SC 9 million units, three times weekly, 52 weeks
	Placebo + interferon	322	60 (18-81)	Placebo	Interferon, SC 9 million units, three times weekly, 52 weeks
CABOSUN	Cabozantinib	79	63 (40-82)	Cabozantinib, PO 60mg, once daily UDP	--
	Sunitinib	78	64 (21-87)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
CALGB 90206	Bevacizumab + interferon	369	61 (NA-NA)	Bevacizumab, IV 10mg/kg D1, D15 of 28 day cycle UDP	Interferon, SC 9 million units, three times weekly UDP
	Interferon	363	62 (NA-NA)	Interferon, SC 9 million units, three times weekly UDP	--
CheckMate 214	Nivolumab + ipilimumab	550	62 (26-85)	Nivolumab, IV 3mg/kg, every three weeks UDP	Ipilimumab, IV 1mg/kg every three weeks UDP
	Sunitinib	546	62 (21-85)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
COMPARZ	Pazopanib	557	61 (18-88)	Pazopanib, PO 800mg, once daily UDP	--
	Sunitinib	553	62 (23-86)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
Escudier 2009	Sorafenib	97	62 (34-78)	Sorafenib, PO 400mg twice daily UDP	--
	Interferon	92	62 (18-80)	Interferon, SC 9 million units, three times weekly UDP	--
Hutson 2013	Axitinib	192	58 (23-83)	Axitinib, PO 5mg, twice daily UDP	--
	Sorafenib	96	58 (20-77)	Sorafenib, PO 400mg twice daily UDP	--
IMmotion 150	Sunitinib	101	61 (25-85)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
	Atezolizumab + bevacizumab	101	62 (32-88)	Atezolizumab, IV 1200mg, once every three weeks UDP	Bevacizumab, IV 15mg/kg once every three weeks UDP
	Atezolizumab	103	61 (27-81)	Atezolizumab, IV 1200mg, once every three weeks UDP	--
IMmotion 151	Sunitinib	461	60 (NA-NA)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
	Atezolizumab + bevacizumab	454	62 (NA-NA)	Atezolizumab, IV 1200mg, once every three weeks UDP	Bevacizumab, IV 15mg/kg once every three weeks UDP
INTORACT	Temsirolimus + bevacizumab	400	59 (22-87)	Temsirolimus, IV 25mg, once weekly UDP	Bevacizumab, IV 10mg/kg D1, D15 of 28 day cycle UDP
	Interferon alfa + bevacizumab	391	58 (23-81)	Interferon alfa, SC 9 million units, three times weekly UDP	Bevacizumab, IV 10mg/kg D1, D15 of 28 day cycle UDP
JAVELIN Renal 101	Avelumab + axitinib	442	62 (29-83)	Avelumab, IV 10mg/kg every two weeks	Axitinib, PO 5mg, twice daily UDP
	Sunitinib	444	61 (27-88)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
KEYNOTE-426	Pembrolizumab + axitinib	432	62 (30-89)	Pembrolizumab, IV 200mg, every three weeks	Axitinib, PO 5mg, twice daily UDP
	Sunitinib	429	61 (26-90)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
Motzer 2007	Sunitinib	375	62 (27-87)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
	Interferon alpha	375	59 (34-85)	Interferon, SC 9 million units, three times weekly UDP	--
TemPa	Pazopanib	35	61 (37-75)	Pazopanib, PO 800mg, once daily UDP	--
	Temsirolimus	34	61 (42-80)	Temsirolimus, IV 25mg, once weekly UDP	--
TIVO-1	Tivozanib	260	59 (23-83)	Tivozanib, PO 1.5mg, once daily UDP	--
	Sorafenib	257	59 (23-85)	Sorafenib, PO 400mg twice daily UDP	--
TORAVA	Bevacizumab + temsirolimus	88	62 (33-83)	Bevacizumab, IV 10mg/kg D1, D15 of 28 day cycle UDP	--
	Sunitinib	42	61 (33-83)	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
	Interferon alfa + bevacizumab	41	62 (40-79)	Interferon alfa, SC 9 million units, three times weekly UDP	Bevacizumab, IV 10mg/kg D1, D15 of 28 day cycle UDP
VEG105192	Pazopanib	290	59 (28-85)	Pazopanib, PO 800mg, once daily UDP	--
	Placebo	145	60 (25-81)	Placebo	--

The network of evidence for all included RCTs in the 1L clear cell feasibility assessment is presented in Figure 2, and outcome availability is summarized in Table 3. The following connected networks for available for the outcomes: 14 RCTs for the base case analysis of ORR (Figure 3), 15 RCTs for the HR analysis of PFS (Figure 4), 14 RCTs for the time-varying HR analysis of PFS (Figure

5), 10 RCTs for the HR analysis of OS (as well as two trials disconnected from the overall network) (Figure 6), 8 RCTs for the time-varying HR analysis of OS (Figure 7), and 12 RCTs for discontinuations due to AEs (Figure 8). Two disconnected networks of three RCTs were available for the analysis of grade 3+ treatment-related adverse events (TRAE) (Figure 9), although only the network included KEYNOTE-426 is included in the analysis. Three trials included only intermediate and poor risk patients, and were excluded from the base case analysis, however their ITT populations were considered for the intermediate and poor risk subgroup analyses.

Table 3: Summary of 1L clear cell outcome availability

Trial ID	Intervention	ORR	PFS		OS		Grade 3+ TRAE	Discont. due to AE
			HR	KM	HR	KM		
ARCC*	Interferon Alfa -- Temsirolimus -- Interferon + Temsirolimus							
AVOREN	Bevacizumab + interferon alfa -- Placebo + interferon alfa	Y	Y	Y	Y	Y		Y
CABOSUN*	Cabozantinib -- Sunitinib							
CALGB 90206	Bevacizumab + Interferon -- Interferon	Y	Y	Y	Y	Y		Y
CheckMate 214	Nivolumab + Ipilimumab -- Sunitinib	Y	Y	Y	Y	Y	Y	Y
COMPARZ	Pazopanib -- Sunitinib	Y	Y	Y	Y	Y		Y
Escudier 2009	Sorafenib -- Interferon	Y	Y	Y				Y
Hutson 2013	Axitinib -- Sorafenib	Y	Y	Y				Y
IMmotion150	Sunitinib -- Atezolizumab + bevacizumab -- Atezolizumab	Y	Y	Y				Y
IMmotion151	Sunitinib -- Atezolizumab + bevacizumab	Y	Y		Y			
INTORACT	Temsirolimus + Bevacizumab -- Interferon alpha + Bevacizumab	Y	Y	Y	Y	Y		Y
JAVELIN Renal 101	Avelumab + Axitinib -- Sunitinib	Y	Y	Y	Y	Y	Y	Y
KEYNOTE-426	Pembrolizumab + Axitinib -- Sunitinib	Y	Y	Y	Y	Y	Y	Y
Motzer 2007	Sunitinib -- Interferon alpha	Y	Y	Y	Y	Y		Y
TemPa*	Pazopanib -- Temsirolimus							
TIVO-1	Tivozanib -- Sorafenib		Y	Y				
TORAVA	Bevacizumab + temsirolimus -- Sunitinib -- Interferon alfa + Bevacizumab	Y	Y	Y				Y
VEG105192	Pazopanib -- Placebo	Y	Y	Y	Y			

Abbreviations: *AE, adverse event; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; KM, Kaplan-Meier curve; AE, adverse event; TRAE, treatment-related adverse event.*
**ARCC, CABOSUN, and TemPa included only intermediate risk and poor risk patients, and were therefore excluded from base case analyses and only considered for inclusion in subgroup analyses.*

Figure 2: Network of evidence for all included randomized controlled trials in 1L clear cell feasibility assessment; all outcomes

Figure 3: Network of evidence for 1L clear cell objective response rate

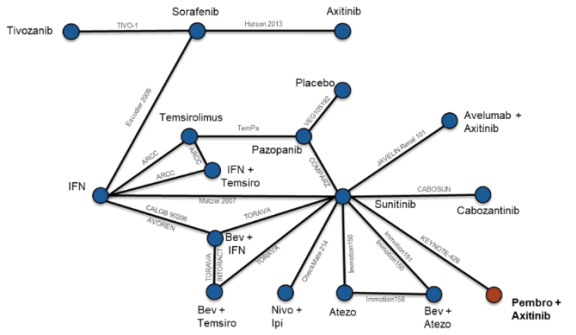


Figure 4: Network of evidence for 1L clear cell progression-free survival; hazard ratios

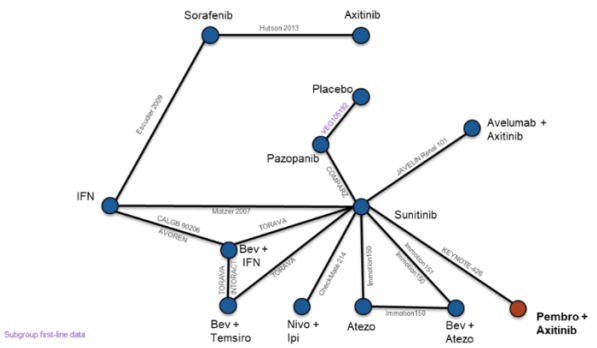


Figure 5: Network of evidence for 1L clear cell progression-free survival; Kaplan-Meier curves

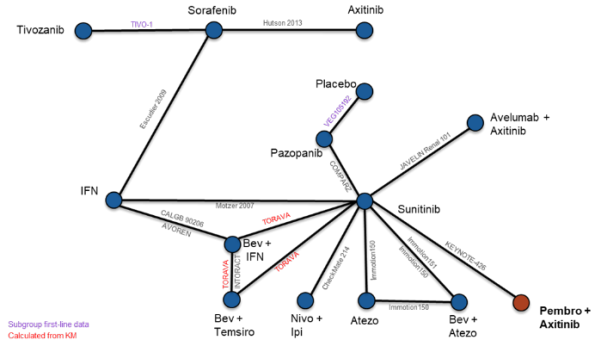


Figure 6: Network of evidence for 1L clear cell overall survival; hazard ratios

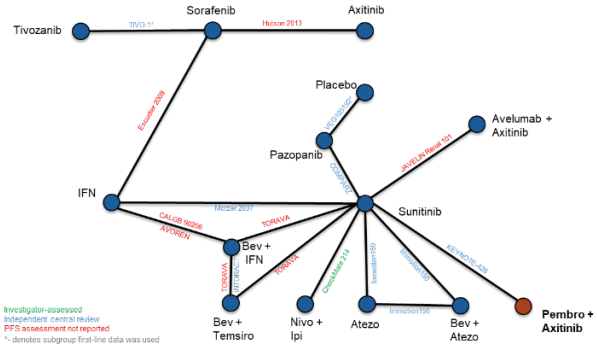


Figure 7: Network of evidence for 1L clear cell overall survival; Kaplan-Meier curves

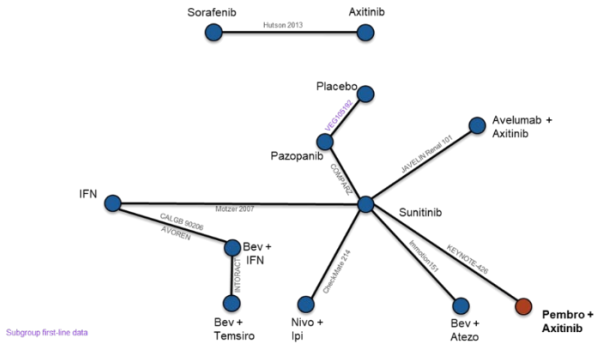


Figure 8: Network of evidence for 1L clear cell discontinuations due to AEs

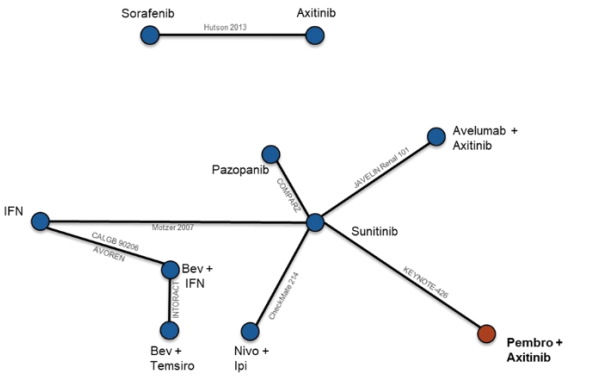
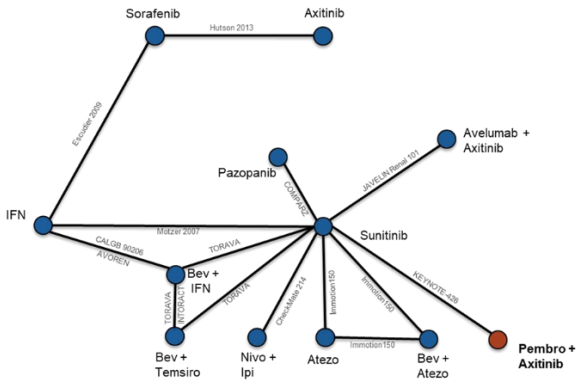
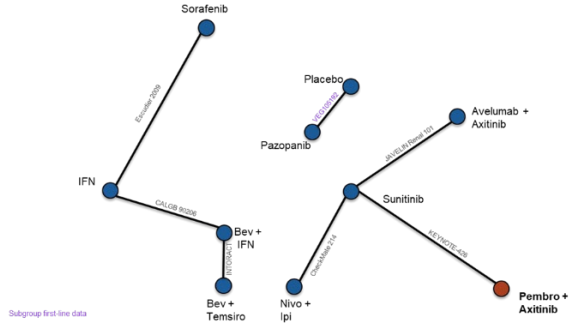


Figure 9: Network of evidence for 1L clear cell grade 3+ TRAEs





a) Results for ORR

The results for the base case analysis of ORR suggested pembrolizumab + axitinib was favoured compared to all competing interventions, except for avelumab + axitinib [OR=0.86, 95% CrI: 0.58-1.27].[20] No subgroup analyses were available for this outcome. The sensitivity analysis of the Canadian context indicated similar results, [redacted]

[24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

b) *Results for PFS*

The results for the base case analysis of PFS using a constant HR (which assumes the proportion hazards assumption is not violated) suggested that treatment with pembrolizumab + axitinib was favoured over all competing interventions [HR range: 0.26 -1.00] except avelumab + axitinib [HR=1.00, 95% CrI: 0.76-1.32] and nivolumab + ipilimumab [HR=0.81, 95% CrI: 0.64-1.03] (Table 4)[20]. Employing fixed-effects, the best-fitting model was the 2nd order FP model with p1=0, p2=0. The results of the time-varying HR analysis (Table 5) showed that pembrolizumab + axitinib was favoured over sunitinib throughout the first 18 months of follow-up. Based on 95% CrIs, pembrolizumab + axitinib was not favoured over avelumab + axitinib and nivolumab + ipilimumab throughout the follow-up. The hazard ratios for sorafenib, axitinib, tivozanib, and bevacizumab + temsirolimus versus sunitinib increased over time. Furthermore, the HRs for nivolumab + ipilimumab versus sunitinib decreased from month 3 to month 18. The report suggested that, although there is evidence the proportional hazards' assumption was violated in certain interventions, the constant HR NMA estimates were more appropriate given the uncertainty in the time-varying HR NMA results.

Results from the sensitivity analysis of the Canadian context were similar. [redacted]

[24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

Table 4: Hazard ratios estimated from fixed-effects network meta-analysis of progression free survival; base case

Sunitinib	**0.56 (0.48, 0.66)**	0.85 (0.70, 1.02)	**0.75 (0.59, 0.94)**	**0.38 (0.25, 0.59)**	0.64 (0.38, 1.06)	**0.49 (0.33, 0.74)**	1.12 (0.96, 1.30)	0.99 (0.72, 1.36)	0.95 (0.82, 1.11)	0.65 (0.40, 1.06)	**1.45 (1.18, 1.78)**	**1.18 (1.02, 1.37)**	**1.45 (1.19, 1.75)**
1.78 (1.51, 2.10)	**IFN-a**	**1.51 (1.34, 1.69)**	**1.33 (1.09, 1.61)**	0.68 (0.43, 1.08)	1.14 (0.70, 1.85)	0.88 (0.61, 1.27)	**2.00 (1.60, 2.49)**	**1.77 (1.23, 2.53)**	**1.70 (1.36, 2.13)**	1.16 (0.74, 1.83)	**2.59 (2.00, 3.36)**	**2.09 (1.69, 2.61)**	**2.58 (2.01, 3.32)**
1.18 (0.98, 1.43)	**0.66 (0.59, 0.74)**	**Bevacizumab+ IFN-a**	0.88 (0.75, 1.04)	**0.45 (0.28, 0.72)**	0.76 (0.46, 1.24)	**0.58 (0.39, 0.86)**	**1.32 (1.04, 1.69)**	1.18 (0.81, 1.69)	1.13 (0.89, 1.44)	0.77 (0.48, 1.24)	**1.72 (1.30, 2.27)**	**1.39 (1.10, 1.77)**	**1.71 (1.31, 2.25)**
1.34 (1.06, 1.70)	**0.75 (0.62, 0.92)**	1.13 (0.96, 1.34)	**Bevacizumab+ Temsirolimus**	**0.51 (0.32, 0.83)**	0.86 (0.51, 1.45)	0.66 (0.44, 1.00)	**1.50 (1.13, 1.99)**	1.33 (0.89, 1.97)	1.28 (0.97, 1.69)	0.88 (0.54, 1.44)	**1.95 (1.43, 2.66)**	**1.58 (1.20, 2.09)**	**1.95 (1.43, 2.63)**
2.63 (1.70, 4.01)	1.48 (0.93, 2.32)	**2.22 (1.39, 3.53)**	**1.96 (1.20, 3.17)**	**Placebo**	1.68 (0.86, 3.25)	1.30 (0.71, 2.32)	**2.94 (1.86, 4.61)**	**2.60 (1.53, 4.44)**	**2.50 (1.68, 3.70)**	1.71 (0.90, 3.23)	**3.81 (2.36, 6.10)**	**3.09 (1.96, 4.85)**	**3.81 (2.39, 6.08)**
1.56 (0.94, 2.61)	0.88 (0.54, 1.43)	1.32 (0.81, 2.18)	1.17 (0.69, 1.97)	0.59 (0.31, 1.17)	**Axitinib**	0.77 (0.56, 1.06)	**1.75 (1.03, 2.99)**	1.56 (0.85, 2.83)	1.49 (0.88, 2.54)	1.02 (0.68, 1.53)	**2.27 (1.31, 3.95)**	**1.84 (1.08, 3.13)**	**2.27 (1.31, 3.92)**
2.03 (1.35, 3.03)	1.14 (0.79, 1.65)	**1.71 (1.16, 2.54)**	1.51 (1.00, 2.29)	0.77 (0.43, 1.40)	1.30 (0.95, 1.78)	**Sorafenib**	**2.27 (1.47, 3.50)**	**2.01 (1.21, 3.36)**	**1.93 (1.26, 2.96)**	**1.32 (1.01, 1.72)**	**2.94 (1.88, 4.61)**	**2.39 (1.55, 3.68)**	**2.93 (1.88, 4.61)**
0.89 (0.77, 1.04)	**0.50 (0.40, 0.63)**	**0.76 (0.59, 0.96)**	**0.67 (0.50, 0.88)**	**0.34 (0.22, 0.54)**	**0.57 (0.33, 0.97)**	**0.44 (0.29, 0.68)**	**Atezolizumab+ Bevacizumab**	0.89 (0.64, 1.21)	0.85 (0.69, 1.06)	**0.58 (0.35, 0.98)**	**1.30 (1.01, 1.67)**	1.05 (0.85, 1.30)	**1.29 (1.02, 1.65)**
1.01 (0.74, 1.38)	**0.56 (0.40, 0.81)**	0.85 (0.59, 1.23)	0.75 (0.51, 1.12)	**0.38 (0.23, 0.65)**	0.64 (0.35, 1.17)	**0.50 (0.30, 0.83)**	1.13 (0.83, 1.55)	**Atezolizumab**	0.96 (0.67, 1.37)	0.66 (0.37, 1.17)	**1.46 (1.00, 2.14)**	1.18 (0.84, 1.69)	**1.46 (1.01, 2.11)**
1.05 (0.90, 1.22)	**0.59 (0.47, 0.74)**	0.89 (0.70, 1.13)	0.78 (0.59, 1.03)	**0.40 (0.27, 0.60)**	0.67 (0.39, 1.14)	**0.52 (0.34, 0.79)**	1.18 (0.95, 1.46)	1.04 (0.73, 1.49)	**Pazopanib**	0.68 (0.41, 1.14)	**1.52 (1.18, 1.96)**	1.23 (1.00, 1.53)	**1.52 (1.19, 1.94)**
1.54 (0.94, 2.48)	0.86 (0.54, 1.35)	1.30 (0.81, 2.06)	1.14 (0.69, 1.86)	0.59 (0.31, 1.11)	0.98 (0.65, 1.48)	**0.76 (0.58, 0.99)**	**1.72 (1.03, 2.86)**	1.53 (0.86, 2.72)	1.46 (0.88, 2.42)	**Tivozanib**	**2.23 (1.30, 3.73)**	**1.81 (1.09, 3.00)**	**2.22 (1.32, 3.74)**
0.69 (0.56, 0.84)	**0.39 (0.30, 0.50)**	**0.58 (0.44, 0.77)**	**0.51 (0.38, 0.70)**	**0.26 (0.16, 0.42)**	**0.44 (0.25, 0.77)**	**0.34 (0.22, 0.53)**	**0.77 (0.60, 0.99)**	**0.68 (0.47, 1.00)**	**0.66 (0.51, 0.85)**	**0.45 (0.27, 0.77)**	**Avelumab+ Axitinib**	0.81 (0.64, 1.04)	1.00 (0.76, 1.32)

0.85 (0.73, 0.98)	**0.48 (0.38, 0.59)**	**0.72 (0.57, 0.91)**	**0.63 (0.48, 0.83)**	**0.32 (0.21, 0.51)**	**0.54 (0.32, 0.92)**	**0.42 (0.27, 0.64)**	0.95 (0.77, 1.17)	0.84 (0.59, 1.19)	0.81 (0.65, 1.00)	**0.55 (0.33, 0.92)**	1.23 (0.96, 1.57)	**Nivolumab+ Ipilimumab**	1.23 (0.97, 1.57)
0.69 (0.57, 0.84)	**0.39 (0.30, 0.50)**	**0.58 (0.45, 0.76)**	**0.51 (0.38, 0.70)**	**0.26 (0.16, 0.42)**	**0.44 (0.26, 0.76)**	**0.34 (0.22, 0.53)**	**0.77 (0.60, 0.99)**	**0.69 (0.47, 0.99)**	**0.66 (0.51, 0.84)**	**0.45 (0.27, 0.76)**	1.00 (0.76, 1.32)	0.81 (0.64, 1.03)	**Pembrolizumab+ Axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 30.74; Deviance: 17.73

Table 5: Time-varying hazard ratios of progression-free survival at select follow-up times for competing interventions versus sunitinib; base case

Mos.	HR vs. sunitinib (95% CrI)												
	Pembro+ Axi	Nivo+ Ipi	Ave+ Axi	Tivo	Pazo	Atezo	Atezo+ Bev	Soraf	Axi	Placebo	Bev+ Tem	Bev+ IFN-a	IFN-a
3	**0.66 (0.51, 0.86)**	1.21 (0.96, 1.52)	**0.68 (0.54, 0.84)**	0.58 (0.23, 1.46)	0.98 (0.80, 1.21)	1.26 (0.69, 2.33)	0.62 (0.31, 1.22)	0.59 (0.25, 1.34)	0.45 (0.17, 1.08)	**2.90 (1.83, 4.59)**	0.93 (0.67, 1.28)	1.06 (0.82, 1.36)	**2.10 (1.66, 2.62)**
6	**0.67 (0.55, 0.82)**	0.91 (0.78, 1.06)	**0.72 (0.57, 0.90)**	1.29 (0.77, 2.15)	1.08 (0.93, 1.27)	0.95 (0.61, 1.45)	0.77 (0.49, 1.19)	**1.67 (1.08, 2.55)**	1.32 (0.77, 2.27)	**2.83 (1.79, 4.46)**	1.19 (0.89, 1.57)	1.06 (0.81, 1.37)	**1.75 (1.33, 2.25)**
9	**0.68 (0.53, 0.86)**	**0.77 (0.66, 0.89)**	0.74 (0.55, 1.00)	**2.06 (1.10, 3.81)**	1.15 (0.96, 1.36)	0.80 (0.48, 1.30)	0.88 (0.57, 1.36)	**3.09 (1.78, 5.18)**	**2.49 (1.26, 4.78)**	**2.79 (1.52, 5.06)**	1.38 (0.98, 1.94)	1.06 (0.76, 1.47)	**1.57 (1.11, 2.17)**
12	**0.68 (0.51, 0.91)**	**0.68 (0.57, 0.81)**	0.76 (0.52, 1.10)	**2.86 (1.25, 6.59)**	1.19 (0.97, 1.46)	0.71 (0.38, 1.28)	0.97 (0.58, 1.62)	**4.76 (2.24, 9.91)**	**3.91 (1.59, 9.25)**	**2.76 (1.32, 5.70)**	**1.53 (1.02, 2.30)**	1.07 (0.71, 1.57)	1.45 (0.97, 2.14)
15	**0.68 (0.49, 0.95)**	**0.62 (0.51, 0.76)**	0.77 (0.50, 1.18)	**3.70 (1.32, 10.42)**	1.23 (0.98, 1.55)	0.64 (0.32, 1.29)	1.04 (0.57, 1.90)	**6.66 (2.61, 16.63)**	**5.54 (1.85, 15.89)**	**2.74 (1.17, 6.29)**	**1.65 (1.04, 2.66)**	1.07 (0.68, 1.66)	1.36 (0.87, 2.13)
18	0.69 (0.47, 1.00)	**0.58 (0.46, 0.72)**	0.78 (0.48, 1.26)	**4.56 (1.38, 15.33)**	1.26 (0.98, 1.64)	0.60 (0.27, 1.30)	1.10 (0.56, 2.19)	**8.76 (2.93, 25.67)**	**7.36 (2.08, 24.96)**	**2.73 (1.05, 6.85)**	**1.77 (1.06, 2.99)**	1.07 (0.65, 1.75)	1.30 (0.80, 2.12)

For the subgroup analysis of 'intermediate and poor risk' patients, the results of the constant HR analysis showed that pembrolizumab + axitinib was favoured over sunitinib [HR=0.67, 95% CrI: 0.53-0.85], but not over cabozantinib or nivolumab + ipilimumab.[15] The results of the time-varying HR analysis showed that pembrolizumab + axitinib was favoured over sunitinib throughout the first 6 months of follow-up. Pembrolizumab + axitinib was not favoured over cabozantinib or nivolumab + ipilimumab throughout follow-up. Although HRs for both pembrolizumab + axitinib and cabozantinib versus sunitinib were relatively consistent from three months to 18 months, HRs for nivolumab + ipilimumab versus sunitinib varied throughout follow-up. Therefore, there is evidence the proportional hazards assumption was violated for nivolumab + ipilimumab versus sunitinib. The report concluded that the constant HR NMA results was considered appropriate although violations to the proportional hazards' assumption were acknowledged. The sensitivity analysis of the Canadian context indicated similar results, [redacted][24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

For the subgroup analysis of 'favourable risk' patients, the results of the constant HR analysis showed that pembrolizumab + axitinib was favoured over IFN-a [HR=0.30, 95% CrI: 0.15-0.60] and bevacizumab+ temsirolimus [HR=0.41, 95% CrI: 0.18-0.98], but not over any other comparators. The results of the time-varying HR analysis showed that pembrolizumab + axitinib was not favoured over sunitinib throughout follow-up.[15] The sensitivity analysis of the Canadian context indicated similar results [redacted][24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

c) *Results for OS*

The results for the base case NMA of OS using a constant HR analysis (which assumes the proportion hazards assumption is not violated) suggested that treatment with pembrolizumab + axitinib was favoured compared to all competing interventions [HR range: 0.43-0.75] except avelumab + axitinib [HR=0.68, 95% CrI: 0.43-1.09] and nivolumab + ipilimumab [HR=0.75, 95% CrI: 0.51-1.09] (Table 6).[20] The best-fitting fixed-effect model was the 2nd order FP model with p1=0, p2=0. The results of the time-varying HR (Table 7) analysis showed that pembrolizumab + axitinib was favoured over sunitinib throughout the first 9 months of follow-up. The HRs for bevacizumab + temsirolimus and IFN-α versus sunitinib decreased over time. The report stated that time-varying HR analyses were considered more appropriate than constant HR results because the proportional hazards' assumption did not hold. Pembrolizumab + axitinib was not favoured over nivolumab + ipilimumab or avelumab + axitinib throughout follow-up. The sensitivity analysis of the Canadian context indicated similar results [redacted][24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

Table 6: Hazard ratios estimated from fixed-effect network meta-analysis of overall survival; base case

Sunitinib	**0.82 (0.67, 1.00)**	0.93 (0.73, 1.18)	0.93 (0.69, 1.25)	1.10 (0.76, 1.60)	1.23 (0.97, 1.58)	1.09 (0.94, 1.26)	1.28 (0.92, 1.78)	**1.41 (1.17, 1.70)**	**1.89 (1.36, 2.63)**
1.22 (1.00, 1.50)	**IFN-a**	**1.13 (1.01, 1.28)**	1.14 (0.91, 1.42)	1.34 (0.88, 2.06)	**1.51 (1.10, 2.07)**	**1.33 (1.04, 1.70)**	**1.56 (1.06, 2.32)**	**1.72 (1.31, 2.27)**	**2.31 (1.57, 3.39)**
1.08 (0.85, 1.36)	**0.88 (0.78, 0.99)**	**Bevacizumab+ IFN-a**	1.00 (0.83, 1.20)	1.18 (0.76, 1.85)	1.33 (0.95, 1.87)	1.17 (0.88, 1.54)	1.38 (0.92, 2.07)	**1.52 (1.12, 2.05)**	**2.03 (1.35, 3.05)**
1.08 (0.80, 1.45)	0.88 (0.70, 1.10)	1.00 (0.83, 1.20)	**Bevacizumab+ Temsirolimus**	1.18 (0.73, 1.91)	1.32 (0.90, 1.96)	1.17 (0.84, 1.64)	1.38 (0.87, 2.15)	**1.52 (1.07, 2.18)**	**2.03 (1.30, 3.18)**
0.91 (0.62, 1.32)	0.75 (0.49, 1.14)	0.85 (0.54, 1.32)	0.85 (0.52, 1.37)	**Placebo**	1.12 (0.72, 1.76)	0.99 (0.70, 1.39)	1.16 (0.71, 1.93)	1.29 (0.84, 1.94)	**1.72 (1.05, 2.82)**
0.81 (0.63, 1.04)	**0.66 (0.48, 0.91)**	0.75 (0.54, 1.06)	0.76 (0.51, 1.11)	0.89 (0.57, 1.38)	**Atezolizumab+ Bevacizumab**	0.88 (0.66, 1.18)	1.04 (0.68, 1.56)	1.14 (0.84, 1.56)	**1.53 (1.01, 2.31)**
0.92 (0.80, 1.06)	**0.75 (0.59, 0.96)**	0.85 (0.65, 1.13)	0.85 (0.61, 1.19)	1.01 (0.72, 1.42)	1.13 (0.85, 1.51)	**Pazopanib**	1.17 (0.82, 1.70)	**1.30 (1.02, 1.64)**	**1.73 (1.21, 2.50)**
0.78 (0.56, 1.09)	**0.64 (0.43, 0.94)**	0.73 (0.48, 1.09)	0.73 (0.46, 1.14)	0.86 (0.52, 1.42)	0.96 (0.64, 1.47)	0.85 (0.59, 1.22)	**Avelumab+ Axitinib**	1.10 (0.75, 1.61)	1.48 (0.92, 2.35)
0.71 (0.59, 0.86)	**0.58 (0.44, 0.76)**	**0.66 (0.49, 0.89)**	**0.66 (0.46, 0.94)**	0.78 (0.52, 1.19)	0.87 (0.64, 1.20)	**0.77 (0.61, 0.98)**	0.91 (0.62, 1.33)	**Nivolumab+ Ipilimumab**	1.34 (0.92, 1.96)
0.53 (0.38, 0.74)	**0.43 (0.29, 0.64)**	**0.49 (0.33, 0.74)**	**0.49 (0.31, 0.77)**	**0.58 (0.35, 0.96)**	**0.65 (0.43, 0.99)**	**0.58 (0.40, 0.83)**	0.68 (0.43, 1.09)	0.75 (0.51, 1.09)	**Pembrolizumab+ Axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 17.51; Deviance: 8.49

Table 7: Time-varying hazard ratios of overall survival at select follow-up times for competing interventions versus sunitinib; base case

	HR vs. sunitinib (95% CrI)						
Mos.	**Pembrolizumab+ Axitinib**	**Nivolumab+ Ipilimumab**	**Avelumab+ Axitinib**	**Pazopanib**	**Bevacizumab+ Temsirolimus**	**Bevacizumab+ IFN-a**	**IFN-a**
3	**0.45 (0.27, 0.72)**	0.83 (0.60, 1.16)	0.82 (0.51, 1.31)	0.82 (0.59, 1.13)	**1.92 (1.08, 3.46)**	1.52 (0.98, 2.38)	**1.93 (1.31, 2.82)**
6	**0.55 (0.39, 0.76)**	**0.79 (0.63, 0.99)**	0.80 (0.57, 1.12)	0.88 (0.70, 1.09)	1.43 (0.98, 2.10)	1.24 (0.93, 1.66)	**1.49 (1.17, 1.91)**
9	**0.61 (0.43, 0.88)**	**0.77 (0.64, 0.93)**	0.79 (0.55, 1.14)	0.91 (0.77, 1.09)	1.20 (0.87, 1.65)	1.10 (0.87, 1.41)	**1.29 (1.05, 1.58)**
12	0.67 (0.44, 1.02)	**0.76 (0.63, 0.91)**	0.79 (0.51, 1.22)	0.94 (0.81, 1.10)	1.06 (0.78, 1.45)	1.01 (0.80, 1.30)	1.16 (0.94, 1.43)
15	0.71 (0.43, 1.17)	**0.75 (0.62, 0.90)**	0.78 (0.47, 1.30)	0.96 (0.83, 1.12)	0.96 (0.69, 1.34)	0.95 (0.74, 1.24)	1.06 (0.85, 1.34)
18	0.75 (0.43, 1.32)	**0.74 (0.60, 0.90)**	0.78 (0.44, 1.38)	0.98 (0.84, 1.14)	0.89 (0.62, 1.28)	0.90 (0.68, 1.21)	0.99 (0.77, 1.29)

For the subgroup analysis of 'intermediate and poor risk' patients, the results of the constant HR analysis showed that pembrolizumab + axitinib was favoured over sunitinib [HR=0.52, 95% CrI: 0.37-0.74], but not over the other comparators.[15] The results of the time-varying HR analysis showed that pembrolizumab + axitinib was favoured over sunitinib throughout the first 9 months of follow-up. The HRs for pembrolizumab + axitinib versus sunitinib increased throughout follow-up. The report concluded that, although there is evidence the proportional hazards' assumption was violated in certain interventions, that constant HR NMA estimates were more appropriate given the uncertainty in the time-varying HR NMA results. The sensitivity analysis of the Canadian

context indicated similar results, [redacted] [24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

For the subgroup analysis of 'favourable risk' patients, the results of the constant HR analysis showed that pembrolizumab + axitinib was not favoured over any of the included comparators [HR range: 0.53-0.73].[15] The results of the time-varying HR analysis showed that pembrolizumab + axitinib was not favoured over sunitinib throughout follow-up. The sensitivity analysis of the Canadian context indicated similar results, [redacted]. [24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

d) Results for discontinuations due to AEs

The results of the fixed-effects NMA (Table 8) showed that pembrolizumab+axitinib had a lower risk of discontinuations due to AEs compared to IFN-a [OR = 0.48, 95% CI: 0.26-0.87], bevacizumab + IFN-a [OR = 0.24, 95% CI: 0.13-0.44], bevacizumab + temsirolimus [OR = 0.18, 95% CI: 0.09-0.36], and nivolumab + ipilimumab [OR = 0.43, 95% CI: 0.26-0.73]. Pembrolizumab + axitinib was not was favoured over the remaining competing interventions. The sensitivity analysis of the Canadian context indicated similar results, [redacted]. [24] *Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*

Table 8: Odds ratios estimated from fixed-effects network meta-analysis for discontinuations due to AEs

Sunitinib	**0.54 (0.35, 0.82)**	**0.27 (0.16, 0.43)**	**0.20 (0.12, 0.35)**	0.50 (0.10, 2.30)	0.77 (0.30, 2.05)	0.63 (0.26, 1.49)	1.55 (0.55, 4.57)	0.78 (0.58, 1.03)	**1.90 (1.23, 3.00)**	**0.48 (0.35, 0.67)**	1.12 (0.75, 1.68)
1.85 (1.21, 2.89)	**IFN-a**	**0.49 (0.38, 0.64)**	**0.38 (0.25, 0.57)**	0.94 (0.19, 3.94)	1.41 (0.60, 3.38)	1.17 (0.43, 3.07)	2.88 (0.93, 9.09)	1.43 (0.86, 2.44)	**3.54 (1.90, 6.60)**	0.90 (0.52, 1.56)	**2.09 (1.15, 3.78)**
3.76 (2.33, 6.11)	**2.03 (1.55, 2.66)**	**Bevacizumab+ IFN-a**	0.76 (0.55, 1.05)	1.91 (0.38, 8.16)	**2.87 (1.18, 7.19)**	2.37 (0.85, 6.40)	**5.85 (1.85, 19.05)**	**2.91 (1.66, 5.13)**	**7.18 (3.75, 13.83)**	**1.83 (1.01, 3.28)**	**4.24 (2.25, 7.97)**
4.95 (2.88, 8.61)	**2.66 (1.77, 4.02)**	1.31 (0.96, 1.82)	**Bevacizumab+ Temsirolimus**	2.52 (0.49, 11.19)	**3.78 (1.48, 9.91)**	**3.13 (1.08, 8.60)**	**7.70 (2.36, 25.72)**	**3.82 (2.07, 7.17)**	**9.47 (4.68, 18.94)**	**2.39 (1.26, 4.51)**	**5.56 (2.82, 11.01)**
1.98 (0.43, 10.10)	1.06 (0.25, 5.15)	0.52 (0.12, 2.62)	0.40 (0.09, 2.04)	**Axitinib**	1.50 (0.48, 5.81)	1.25 (0.22, 7.92)	3.08 (0.48, 22.39)	1.52 (0.33, 8.01)	3.76 (0.77, 20.67)	0.95 (0.20, 5.11)	2.22 (0.47, 11.98)
1.31 (0.49, 3.39)	0.71 (0.30, 1.67)	**0.35 (0.14, 0.85)**	**0.26 (0.10, 0.68)**	0.67 (0.17, 2.08)	**Sorafenib**	0.83 (0.22, 3.00)	2.04 (0.49, 8.52)	1.02 (0.37, 2.72)	2.51 (0.85, 7.09)	0.63 (0.22, 1.74)	1.47 (0.52, 4.12)
1.58 (0.67, 3.88)	0.85 (0.33, 2.33)	0.42 (0.16, 1.18)	**0.32 (0.12, 0.92)**	0.80 (0.13, 4.61)	1.21 (0.33, 4.62)	**Atezolizumab+ Bevacizumab**	2.46 (0.98, 6.82)	1.23 (0.50, 3.10)	**3.02 (1.16, 8.36)**	0.77 (0.31, 1.99)	1.78 (0.69, 4.74)

0.65 (0.22, 1.81)	0.35 (0.11, 1.08)	**0.17 (0.05, 0.54)**	**0.13 (0.04, 0.42)**	0.33 (0.04, 2.08)	0.49 (0.12, 2.06)	0.41 (0.15, 1.02)	**Atezolizumab**	0.50 (0.16, 1.44)	1.22 (0.38, 3.80)	**0.31 (0.10, 0.92)**	0.72 (0.23, 2.19)
1.29 (0.97, 1.72)	0.70 (0.41, 1.16)	**0.34 (0.19, 0.60)**	**0.26 (0.14, 0.48)**	0.66 (0.12, 3.06)	0.99 (0.37, 2.71)	0.82 (0.32, 2.02)	2.00 (0.69, 6.18)	**Pazopanib**	**2.46 (1.45, 4.26)**	**0.62 (0.40, 0.97)**	1.45 (0.89, 2.39)
0.53 (0.33, 0.81)	**0.28 (0.15, 0.53)**	**0.14 (0.07, 0.27)**	**0.11 (0.05, 0.21)**	0.27 (0.05, 1.30)	0.40 (0.14, 1.17)	**0.33 (0.12, 0.86)**	0.82 (0.26, 2.60)	**0.41 (0.23, 0.69)**	**Avelumab + Axitinib**	**0.25 (0.14, 0.44)**	0.59 (0.32, 1.07)
2.07 (1.49, 2.89)	1.11 (0.64, 1.93)	**0.55 (0.30, 0.99)**	**0.42 (0.22, 0.80)**	1.05 (0.20, 5.01)	1.58 (0.57, 4.46)	1.31 (0.50, 3.26)	**3.21 (1.09, 10.00)**	**1.60 (1.03, 2.49)**	**3.95 (2.25, 7.01)**	**Nivolumab+ Ipilimumab**	**2.33 (1.38, 3.91)**
0.89 (0.60, 1.33)	**0.48 (0.26, 0.87)**	**0.24 (0.13, 0.44)**	**0.18 (0.09, 0.36)**	0.45 (0.08, 2.12)	0.68 (0.24, 1.93)	0.56 (0.21, 1.45)	1.38 (0.46, 4.39)	0.69 (0.42, 1.13)	1.69 (0.93, 3.13)	**0.43 (0.26, 0.73)**	**Pembrolizumab+ Axitinib**

Note: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 54.96; Deviance: 31.97

e) Results for Grade 3+ TRAEs

Grade 3+ TRAEs were reported in seven trials, however only three formed a connected network including pembrolizumab + axitinib. The results of the fixed-effects NMA (Table 9) showed that pembrolizumab + axitinib was not favoured over sunitinib or avelumab + axitinib, and that nivolumab + ipilimumab had a lower risk of grade 3+ TRAEs compared with all competing interventions. The sensitivity analysis of the Canadian context indicated similar results. [24]

Table 9: Odds ratios estimated from fixed-effects network meta-analysis for grade 3+ treatment-related AEs

Sunitinib	0.95 (0.72, 1.23)	**2.03 (1.59, 2.59)**	0.81 (0.62, 1.07)
1.06 (0.81, 1.38)	**Avelumab+ Axitinib**	**2.14 (1.51, 3.07)**	0.86 (0.59, 1.26)
0.49 (0.39, 0.63)	**0.47 (0.33, 0.66)**	**Nivolumab+ Ipilimumab**	**0.40 (0.28, 0.58)**
1.23 (0.93, 1.61)	1.16 (0.79, 1.70)	**2.49 (1.72, 3.61)**	**Pembrolizumab+ Axitinib**

Note: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 11.37; Deviance: 5.38

Critical Appraisal of Network Meta-Analysis

The quality of the sponsor-submitted NMA was assessed according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[25] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 10.

Strengths

The NMA was based on a SLR to identify all relevant studies. Overall, the outcome measures assessed were appropriate to address the objectives of the NMA, however limitations to potential differences in outcome definitions are discussed below. Furthermore, the report provided clear methodology and reporting of results. The details from full text included and excluded publications were provided in an appendix. Reasons and sub reasons for the exclusions were stated. Appropriate tables were provided to clearly outline the results. The risk of bias of each individual study was assessed and reported in the provided appendix. The report stated that the

studies were determined to be good quality overall (however some limitations are noted below).
No

The report included analyses using both constant and time-varying HRs, as it appeared that the proportional hazards' assumption was violated for a number of interventions. Furthermore, the HRs were modeled using multiple parametric survival functions and the best fitting model was selected based on the DIC.

The report included analyses that allowed for improved generalizability to the Canadian context. The report provided subgroup analyses of the population for consideration, as well as specific to the Canadian context with currently approved treatments.

Limitations

While a sensitivity analysis of the Canadian context was provided, limitations to the analyses exist. The time-varying approach modelled the data relative to sunitinib only. While sunitinib is one of the drugs that would be considered standard of care in this population, pazopanib and nivolumab + ipilimumab (for intermediate/poor risk patients) are also considered standard of care. It would have been beneficial to have comparisons relative to these treatments as well. A limitation to the report was the lack of clarity on inclusion/exclusion criteria. While a PICO table was provided for the SLR, no table was provided specific to the studies included for the NMA. Exclusion reasons include "updated criteria", and it is not explicitly clear as to when these updates were made in the review and analysis process. Furthermore, the report stated that RCTs that were deemed "sufficiently similar for each population of interest" were synthesized in the NMA. The inclusion is ambiguous as to what would be determined to be sufficiently similar. Additionally, only networks that contained pembrolizumab + axitinib were evaluated in the analysis. Some disconnected networks contained other treatments, however these were excluded from the analyses. The report also provided only the results of the fixed-effects models, as they stated that stable estimates almost all connections in the network were only described by a single trial, and therefore stable estimates of between-study heterogeneity could not be obtained.

Several sources of clinical heterogeneity must be noted. No formal assessment of the heterogeneity was included. Many of the trials did not have baseline data on a number of parameters. While factors considered to be potential treatment effect modifiers were evaluated when possible in subgroup analyses, it must be noted that there was a large amount of missing data for some of the effect modifiers (eg. ECOG), and therefore the subgroup analyses were based on a smaller subset of the original studies of the NMA. This makes it difficult to ascertain whether the study populations are similar. While some factors were accounted for in the subgroup analyses, some factors were not controlled for or further evaluated. This included factors such as previous treatments and various metastases. There was also no mention in the report as to whether the definitions of the outcomes analyzed in the NMA were consistent between studies. There were also some inconsistencies in outcome measurements (eg. PFS being investigator assessed or independently assessed; various methods of calculating HRs depending on data available from the trials). The report also stated that there were unexpected imbalances in drop-outs between groups in a few included trials, but none of these imbalances warranted further investigation, however the reason for this conclusion was unclear. Additionally, there was heterogeneity in study design in that a mix of open-label and double-blind trials was included, as well as some studies allowed cross over between arms.

Limitations occurred in the analysis methods with the assumptions for proportional hazards. While methods were attempted in the analyses to address the issue of non proportional hazards through

alternate approaches, ultimately those analyses had limitations as well that increased the uncertainty of the results. As noted in the report, the time varying analysis of HR showed wider CrIs over the course of follow up, as well as fluctuations in some analyses, which may be due the limited data available at later timepoints. The authors of the report attributed the instability in KM estimates and uncertainty in HR estimates over time to relatively short follow-up where the tails of KM curves may become unstable due to censoring. Furthermore, in some analyses (eg. the base-case analysis of PFS and the subgroup analysis of OS for poor and intermediate risk), the report noted that there was evidence the proportional hazards' assumption was violated, but that the number of events was low, which increased the uncertainty, leading to wider CrIs. The report concluded that the constant HR NMA results was considered appropriate, while acknowledging the violations to the proportional hazards' assumption.

Furthermore, the report stated that results from the AE analysis must be interpreted with caution as varying time on a treatment regimen and follow-up likely lead to inherent differences with respect to rates of discontinuation, which may have resulted in biased estimates. The median treatment duration was variable across and within trials, and that heterogeneity with respect to treatment duration plausibly biased ORs from the NMA. The report also noted that there was variability in TRAE reporting, with some trials reporting only on grade 3/4 TRAEs and one (KETNOTE 426) reporting on grade 3+ TRAEs. They suggest that although grade 5 AEs are unlikely to occur in patients who did not also experience a grade 3/4 AE, the inclusion of grade 3/4 and grade 3+ TRAEs in this analysis may have biased results against KEYNOTE 426.

Table 10: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[25]

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population is relevant as a base case analysis and with the subgroups. The subgroups reflect different patient populations and are in-line with the funding request. Furthermore, the sensitivity analysis was performed to be relevant to the Canadian context.
2. Are any critical interventions missing?	The NMA appeared to include all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	The NMA reported outcomes for ORR, OS, PFS and AEs. It may have benefited from considering outcomes on HRQoL.
4. Is the context (e.g., settings and circumstances) applicable to your population?	The context is applicable to the population. While the global analysis included interventions that were out of context for the Canadian population, a sensitivity analysis was performed with the non-relevant interventions removed. Furthermore, subgroup analyses included the risk groups indicated in the funding request.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR to identify all trials with a clear PICOS criteria. The report of this SLR described the information sources, their search strategy and their selection criteria. However, a PICOS specific to the trials in the NMA was not provided and therefore was not explicitly clear.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the overall analysis form a connected network of RCTs, and most networks for the individual outcomes and subgroups were also connected in a network. There were however some outcomes that could have included disconnected networks, and only networks connected to pembrolizumab + axitinib were analyzed in the subgroup analyses.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of studies was evaluated in the SLR, however there was limited discussed in the conclusions from the NMA. The report did note that the studies were determined to be good quality overall, however most trials were open-label and allocation concealment was unclear in many.

ISPOR Questions	Details and Comments
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated in the risk of bias and quality assessments of the included trials. No selective outcome reporting was found.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	There are differences in the patient and study characteristics from the included studies that may have affected the results of the NMA. Clinical heterogeneity was present in the previous treatments and, disease state between the populations. There was a large amount of missing data for these clinical features, and subgroup analyses could not account for all the features. Furthermore, there was heterogeneity in the inclusion criteria of the trials.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The imbalances in the potential effect modifiers were identified prior to comparing the individual studies, and subgroup analyses were performed where feasible. They were further discussed as a potential limitation to the NMA from the submitter. There was however a large amount of missing data for these effect modifiers, making the networks smaller than the original NMA.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It appeared that methods were used to preserve within-study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	The consistency of both direct and indirect comparisons was evaluated where feasible.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	It is unclear whether both direct and indirect evidence was included in the NMA.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The researchers did attempt to explore imbalances of effect modifiers by conducting sub-group analyses of the identified treatment effect modifiers. There was however a large amount of missing data for these effect modifiers, making the networks smaller than the original NMA.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	The report stated that both fixed and random-effects models were considered, however insufficient trials were available in each network to achieve stable estimates of between-study heterogeneity, so only the fixed-effects results were presented.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable. Only fixed-effects results were presented.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Several subgroup analyses were performed for the identified heterogeneity.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Several networks and tables are presented to indicate the evidence networks with information on the number of RCTs per comparison.
19. Are the individual study results reported?	Individual study results are provided in the appropriate tables.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results of the direct comparisons of the treatments are reported and appropriate tables are included.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CrIs are provided. Comparisons were relative to sunitinib for the time varying results.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No rankings are provided of the reported treatment effects and its uncertainty by outcome.
23. Is the impact of important patient characteristics on treatment effects reported?	The impact of important patient characteristics on treatment effects is not clearly indicated, however subgroup analyses with the

ISPOR Questions	Details and Comments
	characteristics determined to be treatment effect modifiers are performed.
24. Are the conclusions fair and balanced?	The conclusions appear to be fair and balanced. The limitations of the NMA are recognized and reported.
25. Were there any potential conflicts of interest?	Not reported.
26. If yes, were steps taken to address these?	Not applicable.

7.1.3 Summary

In the absence of head-to-head trial data comparing pembrolizumab + axitinib with competing interventions for the first line treatment of metastatic renal cell carcinoma (mRCC), the sponsor submitted a network meta-analysis (NMA). Eighteen trials were identified from the systematic literature review as being relevant to the first-line clear cell mRCC population. The report included results for both constant and time-varying HRs. While there were limitations in all methods included, the results of the constant rate HRs are summarized here

The results of ORR suggested pembrolizumab + axitinib was favoured over all competing interventions, except for avelumab + axitinib. The results of PFS suggested that treatment with pembrolizumab + axitinib was favoured over all competing interventions, except avelumab + axitinib and nivolumab + ipilimumab. The results of OS suggested that treatment with pembrolizumab + axitinib was favoured over all competing interventions, except avelumab + axitinib and nivolumab + ipilimumab. The results of AEs showed that pembrolizumab + axitinib had a lower risk of discontinuations due to AEs compared to IFN-a, bevacizumab + IFN-a, bevacizumab + temsirolimus, and nivolumab + ipilimumab, however pembrolizumab + axitinib was not was favoured over the remaining competing interventions. The results of grade 3+ TRAEs showed that pembrolizumab + axitinib was not favoured over competing interventions. The sensitivity analysis of the Canadian context, which excluded bevacizumab containing regimens, indicated similar results for all outcomes.

Due to the limitations identified, results of the NMA should be interpreted with caution. The relative efficacy of pembrolizumab + axitinib versus other competition interventions remains uncertain for the first line treatment of metastatic renal cell carcinoma.

8. COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

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

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

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Genitourinary Clinical Guidance Panel is comprised of 3 oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(Keytruda* or pembrolizumab* or lambrolizumab* or MK 3475 or MK3475 or Merck 3475 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	14812
2	Axitinib/ or (inlyta* or axitinib* or Axinix* or "ag 013736" or ag013736 or ag 13736 or ag13736 or C9LVQ0YUXG).ti,ab,ot,kf,kw,hw,rn,nm.	5627
3	1 and 2	252
4	3 use cctr	12
5	3 use medall	18
6	*pembrolizumab/ or (Keytruda* or pembrolizumab* or lambrolizumab* or MK 3475 or MK3475 or Merck 3475 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475).ti,ab,kw,dq.	9917
7	*axitinib/ or (inlyta* or axitinib* or Axinix* or "ag 013736" or ag013736 or ag 13736 or ag13736).ti,ab,kw,dq.	2870
8	6 and 7	64
9	8 use oemezd	38
10	(Conference abstract or conference review).pt.	3544473
11	9 not 10	18
12	4 or 5 or 11	48
13	remove duplicates from 12	31
14	9 and 10	20
15	limit 14 to yr="2014 -Current"	20

16	13 or 15	51
17	limit 16 to english language	46

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#5	Search #3 AND #4 Filters: English	3
#4	Search publisher[sb]	410016
#3	Search #1 AND #2	18
#2	Search Axitinib[mh] OR inlyta*[tiab] OR axitinib*[tiab] OR Axinix*[tiab] OR ag 013736[tiab] OR ag013736[tiab] OR ag 13736[tiab] OR ag13736[tiab] OR C9LVQ0YUXG[rn]	903
#1	Search pembrolizumab [Supplementary Concept] OR Keytruda*[tiab] OR pembrolizumab*[tiab] OR lambrolizumab*[tiab] OR MK 3475[tiab] OR MK3475[tiab] OR Merck 3475[tiab] OR HSDB 8257[tiab] OR HSDB8257[tiab] OR Sch 900475[tiab] OR Sch900475[tiab] OR DPT0O3T46P[rn]	2792

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

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

Search: Keytruda/pembrolizumab AND Inlyta/axitinib, renal cell carcinoma

Select international agencies including:

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

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

Search: Keytruda/pembrolizumab AND Inlyta/axitinib, renal cell carcinoma

Conference abstracts:

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

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

Search: Keytruda/pembrolizumab AND Inlyta/axitinib, renal cell carcinoma — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[26]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 Keytruda (pembrolizumab) and Inlyta (axitinib).

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

The search is considered up to date as of Dec 18, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[27] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

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