CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Cabozantinib (Cabometyx) for Renal Cell Carcinoma (Resubmission)

February 20, 2019

DISCLAIMER

Not a Substitute for Professional Advice

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

Liability

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

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

FUNDING

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

INQUIRIES

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

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

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

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature regarding cabozantinib (Cabometyx) for 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 cabozantinib (Cabometyx) for RCC, a summary of submitted Provincial Advisory Group Input on cabozantinib (Cabometyx) for RCC, and a summary of submitted Registered Clinician Input on cabozantinib (Cabometyx) 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 efficacy and safety of cabozantinib (Cabometyx) for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior therapy. The reimbursement request is treatment of patients with advanced renal cell carcinoma (RCC) who have received prior therapy. The Health Canada approved indication is for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior vascular endothelial growth factor (VEGF)-targeted therapy.

Cabozantinib is available in 20 mg, 40 mg and 60 mg film-coated tablets. The recommended dose is 60 mg once daily. Treatment is continued until a patient no longer experiences clinical benefit or until unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one large, multicentre, open-label, phase 3 randomized controlled trial (RCT), METEOR.[1,2] The trial assessed the effect of cabozantinib relative to everolimus in patients with advanced RCC who have been previously treated with at least one previous VEGFR TKI. Patients were included in the trial if they were 18 years of age, had advanced or metastatic clear-cell RCC, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, a Karnofsky performance status of at least 70, received at least one prior VEGFR TKI and must have progressed within 6 months of their most recent VEGFR TKI and within 6 months of randomisation.[3]

A total of 658 patients were randomly assigned on a 1:1 ratio to receive 60mg/d of cabozantinib (n=330) once a day or 10 mg/d of everolimus (N=328).[1,2] Radiological assessments by computed tomography (CT) or magnetic resonance imaging (MRI) were performed at baseline and every 8 weeks for the first 12 months and then every 12 weeks thereafter. Tumour progression was assessed using RECIST 1.1 by a blinded independent review committee (BIRC). Patients continued

to receive treatment as long as they experienced clinical benefit as assessed by the study investigator or until unacceptable toxicity, the need for subsequent anticancer therapy or other withdraw criteria. Patients who progressed as per RECIST1.1 could still continue treatment if the investigator believed that the patient would receive clinical benefit. Cross-over was not permitted.

Patients enrolled in the trial were male (75%), white (81%), had an Eastern Cooperative Oncology Group (ECOG) of 0 (67%) and a favourable (45.5%) or intermediate (41.5%) Memorial Sloan-Kettering Cancer Center (MSKCC) status.[1,2] Additionally, 70.5% of patients had previously treated with one line of VEGFR TKIs and the majority had received sunitinib (63%) or pazopanib (42.5%).[1,2]

Efficacy

The primary outcome in the trial was progression-free survival (PFS) while the secondary outcomes were overall survival (OS) and objective response rate (ORR). Tertiary outcomes included: duration of response (DOR), health-related quality of life (HRQoL) and safety. Disease control rate (DCR) was not assessed in the trial. The METEOR trial was designed to provide adequate power for the assessment of both PFS and OS. For PFS, 259 events (disease progression or death) were required to provide 90% power to detect HR of 0.667 (7.4 months with cabozantinib vs. 5 months with everolimus), using the log-rank test and two-sided significance of 0.05.[3]

The trial was initially designed to conduct one interim analysis in order to assess OS and PFS.[3] However, at the 22-May-2015 data cut-off, OS was immature, and thus the Manufacturer conducted an unplanned interim analysis on 31-Dec-2015. An updated analysis of OS was also conducted on 2-Oct-2016. [34]

At the 22-May-2015 data cut-off, 64.7% of patients treated with cabozantinib had disease progression or died (N=121) relative to 67.0% of patients treated with everolimus (N =128).[5] The median PFS for the cabozantinib was 7.4 months (95% CI: 5.6 to 9.1) and 3.8 months (95% CI: 3.7 to 5.4) in the everolimus group.[1] Cabozantinib was associated with a longer PFS as compared to everolimus (HR: 0.58, 95% CI: 0.45 to 0.75; p-value ≤0.001) (Table 1).[1] Similar estimates were observed at the 31-Dec-2015 analysis (HR: 0.51, 95% CI: 0.41 to 0.62; p-value = ≤0.0001).[2]

The 31-Dec-2015 data cut-off was used for the secondary analysis of OS, which represents a median follow-up of 18.7 months (IQR: 16.1 to 21.1) for patients treated with cabozantinib and 18.8 months (IQR: 16.0 to 21.2) for patients treated with everolimus.[2] Forty-two percent of patients in the cabozantinib group died (N=140) while 55% of patients in the everolimus group died (N =180).[2] The median OS for the cabozantinib group was 21.4 months (95% CI: 18.7 to NE) and 16.5 months (95% CI: 14.7 to 18.8) in the everolimus group.[2] Cabozantinib was associated with a longer OS as compared to everolimus (HR: 0.66, 95% CI: 0.53 to 0.83; p-value = 0.00026) (Table 1).[2] At the later OS analysis of 2-Oct-2016, cabozantinib therapy was associated with a longer OS as compared to everolimus therapy in patients with HCC (HR: 0.70, 95% CI: 0.58 to 0.85; P = 0.0002). [34]

ORR as assessed by BIRC was reported at the 31-Dec-2015 data cut-off using all randomized patients. There was a significantly higher ORR for the cabozantinib group (ORR: 17%, 95% CI: 13 to 22) as compared to the everolimus group (ORR: 3%, 95% CI: 2 to 6) (p-value ≤ 0.0001) (Table 1).[2] No patients in the trial achieved a complete response. The European Medicines Agency (EMA) reported that the DOR for the cabozantinib arm was NE (95% CI: 7.2 months to NE) and it was 7.4 months (95% CI: 1.9 to NE) in the everolimus arm.[5]

Quality of Life

HRQoL was assessed as a tertiary outcome and was measured using the FKSI-19 and the EQ-5D-5L questionnaires. Patient reported outcomes (PROs) were measured at baseline and then every 4 weeks until week 25 where they will be measured every 8 weeks.[3] The baseline completion rates were ≥ 95% for both the FKSI-19 the EQ-5D-5L questionnaires.[6] Additionally, for both treatment groups, the completion rate was ≥ 75% for both questionnaires until Week 49.[6] For the FKSI-19 total score analysis, the difference between treatment arms (i.e. the estimated least-square mean (LSM) in change from baseline) was -0.13 (SD_{pooled}: 9.768; p-value <0.0001); a difference that was considered statistically but not clinically significant (MID ≥ 0.30).[6,7] On the other hand, the difference between treatment arms for the EQ-5D-5L scale (i.e. the estimated LSM in change from baseline) was -0.009 (SD_{pooled}: 0.196; p-value= 0.825) and -0.003 (SD_{pooled}: 16.809; p-value= 0.921) for the EQ-5D-5L VAS scale. [6,7] These differences were not considered statistically significant nor clinically significant (MID ≥ 0.30). Overall, it appears that HRQoL was maintained for patients treated with cabozantinib and everolimus and there were no apparent differences between the FKSI-19 and EQ-5D-5L scales over time.

Safety

A large proportion of patients from the METEOR trial were included in the safety analysis population (99.2%, N = 653).[1,2] There were 311 patients in the cabozantinib arm and 322 in the everolimus arm.

More grade 1-2 adverse event (AEs) occurred in the everolimus arm as compared to the cabozantinib arm (32% vs. 21%) while more grade 3-4 AEs occurred in the cabozantinib group than the everolimus group (71% vs. 60%).[1,2] At the 31-Dec-2015 cut-off, serious adverse events (SAEs) occurred equally across the two treatment arms (cabozantinib: 39% and everolimus: 40%).[2] Similar estimates were reported at the 02-Oct-2016 data cut-off.[4] One treatment-related death occurred in the cabozantinib group but the cause of death was not specified. In the everolimus arm, two treatment-related deaths occurred which were due to aspergillus infection and pneumonia aspiration.[2]

Table 1: Summary of efficacy outcomes in the METEOR trial

Efficacy Outcomes	Cabozantinib	Everolimus
Primary Outcome		
Median PFS[a]	7.4 months (95% CI 5.6 – 9.1)	3.8 months (95% CI 3.7 to 5.4)
Hazard Ratio	0.58 (95% CI 0.45 – 0.75), p<0.001	
Secondary Outcomes		
Median OS[b]	21.4 months (95% CI 18.7 – NE)	16.5 months (95% CI 14.7 – 18.8)
Hazard Ratio †	0.66 (95% CI 0.53 – 0.83), p=0.00026	
ORR[a^]	21% (95% CI 16 – 28)	5% (95% CI 2 – 9)
P value	p<0.001	

[a] In the first 375 patients who underwent randomization as assessed by an independent radiologic review committee; data-cut of date May 22, 2015.
[b] Unplanned second interim analysis data cut-off December 31, 2015.
^confirmed complete and partial response
NE = not estimable
† Met criterion for significance ($p \leq 0.0163$) from the prespecified alpha spending function

Data sources: Choueiri et al (2015) and Choueiri et al (2016)[1,2]

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

From a patient perspective, most patients find current drugs to be generally tolerable. Recent availability of immunotherapies have been an important breakthrough, but patients would like more information on the risk associated with these newer agents as they are known to causes unexpected and sometimes serious side effects. Eventual resistance to first-line agents is almost certain in advanced RCC. About a third of patients providing input indicated the reasons for ending treatment as being due to side effects of treatment and not disease progression.

Patients value having a choice of treatment options (including opportunity to inform choice based on different drug's known side effects), and that current treatment options are not effective for everyone and can be difficult to access. Patients ranked access to drugs that have greater effect on slowing or stopping the spread of kidney cancer in the body (metastasis) as a top priority. Generally, there is a need for improved therapies that do more to improve the outlook for patients with advanced disease, a need for effective predictive and prognostic biomarkers to guide treatment along and a need to better detect disease at earlier stages. There is also a need for treatments that control or overcome treatment resistance mechanisms for advanced disease, and for treatments with greater effectiveness on bone metastases. Patients rank a need for drugs that have greater effect on slowing or stopping the spread of kidney cancer in the body (metastasis) with highest priority.

Please see Section 3 for a summary of specific input received from the patient advocacy groups.

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:

- Axitinib and nivolumab are the current standard of care in second line treatment, and if axitinib is used as a second-line treatment, nivolumab is available as a third line treatment if patient remains good performance status
- Place in therapy and sequencing with currently available treatments and upcoming treatments
- Definition of treatment until patient no longer benefits and clarity on discontinuation criteria

Economic factors:

- Cost effectiveness compared to axitinib and nivolumab as second line therapies and cost effectiveness in the clinical setting where nivolumab is third line treatment
- Unknown and potentially long duration of therapy

Please see Section 4 for a summary of specific input received from the Provincial Advisory Group.

Registered Clinician Input

One clinician input was provided for cabozantinib for the treatment of patients with advanced RCC who have received prior therapy. Input was provided as a joint submission with two clinicians and a pharmacist, who will be referred to as the health professionals throughout the summary. Their input is summarized below.

The health professionals identified cabozantinib as being provided to patients as a second- or further line of therapy. The improvements in PFS and OS, regardless of the fact that some patients had multiple lines of previous therapy in the METEOR trial, was highlighted. However, the toxicity of cabozantinib was noted as a potential challenge, and was mentioned to be comparable to other TKI therapies. While cabozantinib has not been compared to treatments, such as nivolumab or axitinib, the clinician input did suggest the superiority of cabozantinib over everolimus.

Please Section 5 for a summary of specific input received from the registered clinicians.

Summary of Supplemental Questions

Critical appraisal of a manufacturer submitted network meta-analysis (NMA), which provides evidence of the efficacy of cabozantinib as compared to other active therapies in patients with advanced RCC in the second-line setting.

See section 7.1 for more specific 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 Cabozantinib

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (METEOR trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Performance Status</td><td>Patients were enrolled in the trial if they had a Karnofsky Performance Status (KPS) score of ≥ 70%. Eligibility criteria was not influenced by ECOG status.

Baseline Characteristics
<table>
<tr><th></th><th>Cab</th><th>Eve</th></tr>
<tr><td>KPS</td><td></td><td></td></tr>
<tr><td>70</td><td>29 (8.8%)</td><td>2 (6.7%)</td></tr>
<tr><td>≥80</td><td>301 (91%)</td><td>306 (93%)</td></tr>
<tr><td>ECOG</td><td></td><td></td></tr>
<tr><td>0</td><td>226 (68%)</td><td>217 (66%)</td></tr>
<tr><td>1</td><td>104 (32%)</td><td>111 (34%)</td></tr>
</table>
Subgroup Analyses
<table>
<tr><th></th><th>Cab/Eve</th><th>HR for OS</th><th>Cab/Eve</th><th>HR for PFS</th></tr>
<tr><td colspan="5">KPS (Not reported)</td></tr>
<tr><td colspan="5">ECOG</td></tr>
<tr><td>0</td><td>81/105</td><td>0·65 (0·49-0·87)</td><td>114/137</td><td>0·46 (0·36-0·59)</td></tr>
<tr><td>1</td><td>59/75</td><td>0·72 (0·51-1·02)</td><td>66/77</td><td>0·64 (0·46-0·90)</td></tr>
</table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Cabozantinib 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 2 are treated with tyrosine kinase inhibitors such as sunitinib and have shown a good benefit although these patients were initially excluded from the pivotal studies.</td></tr>
<tr><td>Histological Subtype</td><td>Key inclusion criteria in the METEOR trial required that patients have documented histological or cytological diagnosis of RCC with a clear-cell component.</td><td>Do the trial results apply to patients with non-clear cell histology?
Why (why not)?</td><td>Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that cabozantinib will have activity in non-clear cell RCC. Cabozantinib should therefore be made available to patients with non-clear cell histology.</td></tr>
<tr><td>Metastatic Sites</td><td>Patients were excluded from the trial if they had known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization.</td><td>Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g.,</td><td>In clinical practice, patients with controlled brain metastases are treated the same way as patients without brain metastases. Therefore these patients should be eligible for treatment with cabozantinib. However, patients with symptomatic uncontrolled brain metastases should first be treated with</td></tr>
</table>

Domain	Factor	Evidence (METEOR trial)	Generalizability Question	CGP Assessment of Generalizability
			Canadian clinical practice, patients without the factor, etc.)?	radiotherapy and/or surgery and have stable brain metastases before eligibility of cabozantinib treatment.
Intervention	Line of therapy	Patients must have received at least one VEGFR-targeting TKI (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib).	Are the results of the trial generalizable to other lines of therapy	The current evidence supports the use of cabozantanib as second- or third-line therapy in patients with clear cell or clear cell component carcinoma with at least one prior TKI, but could have had exposure to other therapies including prior immunotherapy or mTOR inhibitor.
Comparator	Standard of Care	Everolimus is not a standard of care in Canada	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	The results of the NMA indicate that patients on cabozantinib had a greater likelihood of PFS and OS as compared to those treated with the other comparators (everolimus and nivolumab). The overall conclusions of the NMA are limited because there were considerable differences in the study design and baseline population characteristics of the included studies. Therefore, the NMA should be interpreted with caution. The submitter also made an assumption that axitinib has a similar efficacy to everolimus. The CGP agreed that this is justified by available phase III evidence as well as the available evidence from clinical practice on the efficacy and safety of axitinib and everolimus.

2.2 Interpretation

The management of mRCC has seen significant changes in the past decade with advances in our basic understanding of disease biology and immunology translating into the development of a number of new therapeutic approaches. Angiogenesis inhibitors, mTOR inhibitors and most recently novel checkpoint inhibitors have shown both efficacy and tolerability and significantly changed the therapeutic landscape in this disease.

Until recently, the most commonly used first-line treatment options were the oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) Sunitinib and Pazopanib.[19,20] However, based on the recent CHECKMATE 214 trial, showing superiority of the combination of the CTLA4 checkpoint inhibitor, (ipilimumab) and the PD1 checkpoint inhibitor (nivolumab) over Sunitinib in patients with intermediate or poor risk disease, this is quickly becoming a new first line option in this patient population.

In patients progressing on first line sunitinib or pazopanib, everolimus and Axitinib have been the most commonly used second line agents.[22,23] Both drugs were approved based on a modest progression-free survival (PFS) benefit, but no overall survival (mOS) benefit. For everolimus, PFS was 4.9 months vs. 1.9 months for placebo and for axitinib PFS was 4.8 months vs. 3.4 months for sorafenib. More recently, the checkpoint inhibitor Nivolumab, was shown to be superior to everolimus in the CHECKMATE 025 trial. The median OS for nivolumab was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) for Nivolumab versus 19.6 months (95% CI, 17.6 to 23.1) for everolimus which met the pre-specified criterion for superiority. The objective response rate was higher with nivolumab compared to everolimus (25% vs. 5%; odds ratio 5.98; 95% CI, 3.68 to 9.72; P<0.001), but the PFS was similar. Despite significant advances, as yet, none of these treatments is curative, underscoring the need for novel treatment strategies.

In particular, strategies aimed at overcoming resistance mechanisms to current agents may be particularly effective. One of these agents is Cabozantanib, an oral, small-molecule tyrosine kinase inhibitor that targets the VEGFR as well as the MET and AXL pathways, each of which has been implicated in both the pathogenesis of mRCC and in the development of resistance to antiangiogenic drugs. In a randomized, open-label, phase 3 trial, METEOR, cabozantinib was compared against everolimus in mRCC patients progressing after VEGFR-targeted therapy. Patients with known brain metastases that were adequately treated and stable were eligible for the METEOR trial. There was no limit on the number of prior therapies. In total 658 patients were randomized to cabozantinib at a dose of 60 mg daily or everolimus at a dose of 10 mg daily. Notably, at the time the METEOR trial was designed, everolimus was the standard of care and the most appropriate comparator. Since the start of the METEOR trial, the availability of new data has shifted treatment practice with axitinib and nivolumab currently being considered the most appropriate comparators.

The primary endpoint was PFS. Secondary efficacy end points were ORR and OS. Median PFS for Cabozantanib was robust at 7.4 months compared to 3.8 months with everolimus. The rate of progression or death was 42% lower with cabozantinib than with everolimus (HR, 0.58; 95%CI 0.45 to 0.75; P<0.001). The ORR was 21% with cabozantinib and 5% with everolimus (P<0.001). At the interim analysis, OS was longer with cabozantinib than with everolimus (HR 0.67; 95% CI, 0.51 to 0.89; P=0.005) but did not cross the boundary for significance at the interim analysis. At a later OS analysis, the median OS was 21.4 months with cabozantanib and 17.1 months with everolimus (HR: 0.70, 95% CI: 0.58 to 0.85; P = 0.0002). Adverse events were managed with dose reductions; doses were reduced in 60% of patients on cabozantinib and in 25% of those on everolimus. Discontinuation of study treatment owing to adverse events occurred in 9% on

cabozantinib and in 10% on everolimus. Taken together, the results of the METEOR study, would support the use of cabozantanib in second/third line mRCC patients.[1] Quality of life was measured in the METEORR trial and overall, it appears that HRQoL was maintained for patients treated with cabozantinib and everolimus and there were no apparent differences between the FKSI-19 and EQ-5D scales over time.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to cabozantanib in the second-line / third-line treatment of advanced and metastatic RCC based on one high-quality randomized controlled trial that demonstrated a clinically meaningful and statistically significant benefit in PFS, ORR and a trend towards improved OS for cabozantanib compared with everolimus.

In making this conclusion the CGP also considered the following:

- While significant advances have been achieved in the treatment of mRCC, it remains an incurable disease. Approximately one quarter of patients with RCC present with metastases at diagnosis and at least one-half of all patients will eventually develop advanced disease
- Currently, for patients progressing on first line therapy with Sunitinib or Pazopanib, second line options include nivolumab, everolimus or axitinib with the latter two drugs approved based on a PFS benefit only. Sorafenib is a treatment option that is not used in Canada. None of these options is considered curative, and eventually patients will progress despite them. There is therefore an urgent need for novel treatment options with a different mechanism of action.
- The current evidence supports the use of cabozantanib as second- or third-line therapy in patients with clear cell or clear cell component carcinoma with at least one prior TKI, but could have had exposure to other therapies including prior immunotherapy.
- With the availability of the combination of nivolumab plus ipilimumab in the front line setting, the CGP anticipates that patients will be treated with a TKI second line and then be eligible for cabozantinib in the third line setting. Although acknowledging the rapidly changing treatment landscape for RCC, the CGP noted that patients who were previously treated with sunitinib or pazopanib in the front line setting may qualify for cabozantinib or nivolumab second line, cabozantinib or nivolumab third line (depending on which agent was used second line) and everolimus or axitinib fourth line. For patients treated with nivolumab plus ipilimumab in the front line setting, second line agents may include sunitinib or pazopanib, cabozantinib third line and everolimus or axitinib in the fourth line setting.
- The CGP agreed that cabozantinib can be used for the treatment of patients who have previously been treated with an MTOR inhibitor, noting that this will be in few instances. It is also reasonable to use cabozantinib in patients previously treated with an MTOR inhibitor and who are not eligible for nivolumab.
- The CGP further agreed that patients currently on everolimus and who have not had disease progression should not switch to cabozantinib but rather should wait until disease progression. The CGP noted that if a patient is tolerating the agent well, they should continue as there is no guarantee the next treatment will work. The CGP do however agree that patients intolerant to everolimus should receive cabozantinib.
- As per the METEOR trial, patients can continue on cabozantinib beyond disease progression if they are deriving clinical benefit, based on the judgement of the treating oncologist.
- Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that cabozantinib will have activity in non-clear cell RCC. Cabozantinib should therefore be made available to patients with non-clear cell histology.
- The results of the submitted NMA indicate that patients on cabozantinib had a greater likelihood of PFS and OS as compared to those treated with the other comparators (everolimus and nivolumab). The overall conclusions of the NMA are limited because there were considerable

differences in the study design and baseline population characteristics of the included studies. Therefore, the NMA should be interpreted with caution.

- The submitter also made an assumption that axitinib has a similar efficacy to everolimus. The CGP agreed that this is justified by available phase III evidence as well as the available evidence from clinical practice on the efficacy and safety of axitinib and everolimus.
- Although the CABOSUN first-line trial, comparing cabozantanib to sunitinib in intermediate- or poor-risk mRCC has also been reported, the CGP agreed that the use of cabozantinib in the front line setting is out of scope for this review. The CGP agreed that the data would need to be fully assessed before a decision can be made on the efficacy and safety of cabozantinib in the first line setting.

2 BACKGROUND CLINICAL INFORMATION

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

2.4 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6600 new cases and 1,900 deaths due to the disease.[8] About 90% of kidney cancers are renal cell cancers (RCC), which are genetically and histologically distinctly different from carcinomas arising from the renal pelvis, which are known as urothelial carcinomas (UC). About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers and include papillary and chromophobe subtypes amongst others. At presentation 75% of patients with RCC will have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases), while about 25% are already metastatic. Of the patients diagnosed with localized disease, 30-50% of patients will eventually relapse and metastasize. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly to 50-60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured.[9]

Metastatic RCC is considered refractory to both conventional cytotoxic chemotherapy and conventional radiation therapy. Historically, older immunotherapy approaches like cytokines such as interferon or interleukin were the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit and toxicity was an issue. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[10-12] several key prognostic factors have been identified in patients with metastatic disease that can divide metastatic patients into favourable, intermediate or poor risk groups. The most commonly used classification for mRCC in the era of immunotherapy was the MSKCC criteria which include the presence or absence of five distinct risk factors (performance status, lactate dehydrogenase, corrected calcium, hemoglobin, and time from diagnosis to treatment). This classification has been used both in routine practice to determine prognosis and as part of the eligibility criteria for clinical studies. More recently, the IMDC (The International Metastatic Renal Cell Carcinoma Database Consortium) criteria which better reflects treatment with targeted agents has come into regular use and for the purposes of clinical trials.[13-15]

Advances in our understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents), in particular for the clear-cell subtype of RCC, have resulted in the availability of a number of new treatment options for patients with metastatic RCC. Clear-cell carcinomas are characterized by the presence of inactivating mutations in the von-Hippel-Lindau gene. Loss of functional VHL protein results in the activation of pro-angiogenic and growth factor pathways via constitutive stabilization of the alpha subunits of a group of transcriptionally active proteins called the hypoxia-inducible factors (HIF).[16] HIF plays a central role in renal tumorigenesis by acting as a transcription factor for genes that are involved in angiogenesis, tumor cell proliferation, cell survival and progression, metastatic spread, apoptosis and glucose metabolism. The phosphatidylinositol-3 kinase (PI3K)-AKT-mTOR signal transduction pathway is also involved in controlling HIF. Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR pathways. Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and also have a different toxicity profile.

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

2.5 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced disease. There is currently no role for neoadjuvant therapy. Studies evaluating the use of adjuvant therapy have shown mixed results. But, on the basis of the recent S-TRAC study evaluating adjuvant sunitinib in high risk RCC patients, which showed a disease-free survival benefit, despite excess toxicity, the FDA has approved adjuvant sunitinib in high risk patients.[17]

In the setting of metastatic disease, until the introduction of targeted therapies, immunotherapy (cytokines) with low dose interferon-α, low dose interleukin-2 or high dose interleukin-2 represented the standard of care. Although these agents were helpful for a small subset of patients, the majority of patients derived no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity. Targeted therapies have largely replaced older immunotherapy as standard treatment for patients with metastatic disease and today, high-dose interleukin-2 is only considered for a highly selected, very small subgroup of patients, while low-dose interferon and interleukin-2 as single agents are not recommended at all.[18]

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

Current treatment landscape:

Sunitinib and pazopanib, both small molecule tyrosine kinase inhibitors of the vascular-endothelial-growth-factor receptor are considered the standard treatment options in the first-line setting.[19,20] Sunitinib demonstrated a more than doubling in progression-free survival (PFS) compared to the standard of care at the time, interferon. Sunitinib was also the first drug to lead to a median overall survival of more than 2 years in the metastatic setting. Pazopanib was shown to be non-inferior to sunitinib in a large randomized phase III trial. For poor risk patients (according to the MSKCC criteria) the mTOR inhibitor temsirolimus, given intravenously once a week, was tested in a randomized trial against interferon and demonstrated superior overall survival outcomes as compared to interferon alone or the combination of both drugs. Temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria.[21] Based on the recent CHECKMATE 214 trial, showing superiority of the combination of the CTLA4 checkpoint inhibitor, (ipilimumab) and the PD1 checkpoint inhibitor (nivolumab) over Sunitinib in patients with intermediate or poor risk disease, this is quickly becoming a new first line option in this patient population.

Second Line

After failure of first-line TKI therapy, everolimus, an oral mTOR inhibitor and axitinib, a VEGFR-TKI have both been evaluated and were approved based on a PFS benefit.[22-25] In the RECORD1 trial in patients failing at least one prior line of TKI therapy Everolimus showed a significant PFS benefit over placebo (4.9 vs.1.9 months; HR 0.32).[24] In the AXIS study, in a similar population, Axitinib showed a PFS benefit over sorafenib with median a PFS of 6.7 vs 4.7 months (HR 0.67) in the overall group and 4.8 vs 3.4 months (HR 0.74) in sunitinib pretreated patients. Neither of these studies demonstrated a clear overall survival benefit.

Nivolumab is a novel fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor, that blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Blocking this interaction leads to antitumor response via activation of an immune response. Nivolumab was tested against Everolimus in a large open-label phase III study (Checkmate 025) of 821 mRCC patients failing at least one line of TKI therapy. The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The confirmed response rates were 21.5% versus 3.9%; median durations of response were 23.0 versus 13.7 months[26,27]. At the time the METEOR trial was designed, pivotal trial under review in this report, everolimus was the standard of care and the most appropriate comparator. Since the start of the METEOR trial, the availability of new data has shifted treatment practice with axitinib and nivolumab currently being considered the most appropriate comparators.

Although now approved in second line, there is still a majority of patients that will not respond to Nivolumab, or will respond and subsequently progress, for whom there are no curative options, underscoring the need for new treatment strategies.[28] Strategies based on overcoming resistance mechanisms to current agents maybe particularly effective. One of these agents is Cabozantanib. This is an oral small molecule inhibitor of multiple tyrosine kinase receptors with activity toward VEGF receptor 2 (VEGFR-2) and MET (hepatocyte growth factor receptor), but also targets RET (rearranged during transfection), KIT (mast/stem cell growth factor receptor), AXL, TIE2 (angiopoietin receptor) and FLT3 (Fms-like tyrosine kinase), which are important mediators of tumor cell survival, metastasis and tumor angiogenesis.

2.6 Evidence-Based Considerations for a Funding Population

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

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell histology or clear cell component
- Failure of one or more prior lines of therapy, including one or two prior TKIs and immunotherapy.

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

2.7 Other Patient Populations in Whom the Drug May Be Used

Patients with non-clear cell renal cell carcinoma represent a particularly difficult group. Non-clear cell renal cell carcinoma includes papillary, collecting duct, chromophobe and a

number of other kidney cancer subtypes. Due to the heterogeneity and small patients numbers larger studies are extremely difficult to complete. Today, most of these patients are treated according to clear cell cancer guidelines despite the lack of large randomized studies.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group provided input on cabozantinib for advanced renal cell carcinoma and their input is summarized below: Kidney Cancer Canada (KCC). This patient input provided by KCC was provided to pCODR on behalf of a previous review for cabozantinib for RCC. The current pCODR review for cabozantinib will be reusing the same patient input provided by KCC.

Information from two surveys are provided in the following input. First, KCC conducted an online survey of patients and caregivers from September 19, 2017 to October 4, 2017 to assess the challenges kidney cancer patients and caregivers face as a result of the disease. KCC also assessed the experience and expectation patients have with therapies used to treat kidney cancer, in particular the treatment under review - cabozantinib. 187 patients and caregivers responded to this survey. Additionally from June 15 to August 31, 2016 KCC conducted a cross-Canada survey to identify the unique information, support and treatment access needs of patients living with kidney cancer and their caregivers. 465 patients and caregivers responded to this survey.

Where available, the geographic location of individuals providing input and the type of patients or caregiver providing input are categorised below.

September 19, 2017 to October4, 2017 Online Survey, n=187	
Country	**Number of patients**
Canada (across 9 Provinces)	156 (83%)
US	19 (10%)
UK	6 (3%)
Australia	2 (1%)
Ireland	1 (<1%)
India	1 (<1%)
South Africa	1 (<1%)
New Zealand	1 (<1%)
September 19, 2017 to October4, 2017 Online Survey, n=187	
Living with kidney cancer	68 (36%)
Kidney cancer survivors	67 (36%)
Caregivers	52 (28%)
Experience with cabozantinib	13 (7%)
June 15 – August 31, 2016 Cross-Canada Survey, n=465	
Patients	368 (79%)
caregivers	97 (21%)

Both surveys contained the use of free-form commentary, scoring options and limited closed questions. This report reflects the results of these surveys as well intelligence and insights KCC garnered from more than a decade of experience in patient support, research and advocacy in Canada related to kidney cancer, and through its participation in the global collaboration of patient organisations known as the International Kidney Cancer Coalition (iKCC).

From a patient perspective, most patients find current drugs to be generally tolerable. Recent availability of immunotherapies have been an important breakthrough, but patients would like more information on the risk associated with these newer agents as they are known to causes unexpected and sometimes serious side effects. Eventual resistance to first-line agents is almost certain in advanced RCC. About a third of patients providing input indicated the reasons for ending treatment as being due to side effects of treatment and not disease progression.

Patients value having a choice of treatment options (including opportunity to inform choice based on different drug's known side effects), and that current treatment options are not effective for everyone and can be difficult to access. Patients ranked access to drugs that have greater effect

on slowing or stopping the spread of kidney cancer in the body (metastasis) as a top priority. Generally, there is a need for improved therapies that do more to improve the outlook for patients with advanced disease, a need for effective predictive and prognostic biomarkers to guide treatment along and a need to better detect disease at earlier stages. There is also a need for treatments that control or overcome treatment resistance mechanisms for advanced disease, and for treatments with greater effectiveness on bone metastases. Patients rank a need for drugs that have greater effect on slowing or stopping the spread of kidney cancer in the body (metastasis) with highest priority.

Information was collected from 13 patients with experience using cabozantinib as single-agent therapy. This included 5 Canadian patients. Patients who had experience using cabozantinib indicated that it was effective in most cases to control their cancer, with relatively fair tolerability and impact on their quality of life. Patients rated the side effect profile and tolerability of cabozantinib to be similar to previous therapies they had received. Some side effects reported by patients included diarrhea, fatigue, hand-foot syndrome, mouth sores, and others. Four respondents reported being aware of metastases occurring in their bones, all of whom experienced associated complications, such as fractures, spinal cord compression, bone pain or hypercalcemia. Patients also reported experiencing shrinkage of tumours and greater control over their metastases due to cabozantinib. Based on quotes provided by respondents, cabozantinib provided patients with greater treatment options and an opportunity to potentially prolong their lives.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Renal Cell Carcinoma

KCC did not provide any direct data from patients or caregivers regarding their experiences with RCC. However, KCC stated that there is currently no known cure for metastatic renal cell carcinoma (mRCC), and that experiencing a complete response to treatment with a single agent is rare. While some first line treatments are effective at halting the progression of RCC, patients eventually experience resistance; KCC stated that more effective treatments in further lines of therapy are greatly needed to help overcome the drug resistance. KCC posits the following unmet needs in mRCC: a lack of suitable or effective treatments for all patient subgroups, treatments that prevent progression to other parts of the body, especially progression to bones, and poor control of skeletal-related events (SREs). KCC stated that approximately 85% of patients experience SREs, such as bone pain, fractures and spinal cord compression, which can result in hospitalizations, surgery leading to great burden on the healthcare system in addition to burden experienced by the patient.

3.1.2 Patients' Experiences with Current Therapy for Renal Cell Carcinoma

In the 2016 Cross-Canada survey, 33% and 29% of patients who stopped a first or second-line treatment, respectively reported that the reasons for ending treatment were due to side effects of treatment and not disease progression.

Patients and caregivers were asked, "What therapies have you used to treat your kidney cancer?" Among 105 respondents treatments used included the following:

Treatment	Number of patients
Sunitinib	87
Temsirolimus	4
Everolimus	20

Treatment	Number of patients
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 choice/options throughout their care pathways. Full results for this question are presented in the table below:

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

In previous patient input submissions provided to pCODR (nivolumab 2016, axitinib 2012, pazopanib 2011), KCC reported extensively on various aspects of patient experience with current treatments. The recurring themes in these surveys include 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, and
- Current treatment options are not effective for everyone and can be difficult to access.

3.1.3 Improved Outcomes

Overall, KCC recognizes the advantages and disadvantages of different treatments for RCC, and the different responses patients can exhibit to the same drug. Based on this, when assessing the value of a new drug, KCC stresses the overall importance of treatment choice and patient preference. Furthermore, for patients who find a specific prescribed drug intolerable, treatment alternatives within that line of therapy are extremely important.

KCC indicated a number of gaps present in the management of RCC, including need for improved therapies to improve outlook for patients with advanced disease, more effective predictive and prognostic biomarkers to guide treatment along and a need to better detect disease at earlier stages, treatments that control or overcome treatment resistance mechanisms for advanced disease, and for treatments with greater effectiveness on bone metastases.

Patients and caregivers were asked to rank their top priorities on a scale of 1-5. The questions were close-ended containing 5 randomized (RCC) treatment priority options. Results are presented below:

	1	2	3	4	5	TOTAL	SCORE
We need drugs that have greater effect on slowing or stopping the spread of kidney cancer in the body (metastisis)	23.94% 34	25.35% 36	17.61% 25	16.20% 23	16.90% 24	142	3.23
We need ways of detecting kidney cancer earlier (screening)	40.28% 58	10.42% 15	6.94% 10	8.33% 12	34.03% 49	144	3.15
We need better ways to identify the best drug treatment for each individual patient/disease situation (biomarkers)	16.06% 22	24.09% 33	24.09% 33	19.71% 27	16.06% 22	137	3.04
We need drugs that do better at delaying disease progression	7.19% 10	18.71% 26	26.62% 37	32.37% 45	15.11% 21	139	2.71
We need drugs with fewer side effects than currently available drugs (typical side effects of current drugs include: diarrhea, fatigue, nausea, hypertension, inflammation of mouth and lips, and swelling/numbness of hands and feet)	5.76% 8	15.83% 22	23.02% 32	22.30% 31	33.09% 46	139	2.39

The highest ranked overall priority was a need for drugs to better stop or slow the spread of kidney cancer (score=3.23).The next two highest ranked priorities were for improved screening (score=3.15), and for biomarkers/personalized treatment (score=3.04). KCC noted that therapies based on biomarkers/personalised medicine are not currently available in RCC. The next ranked options were, in order, drugs that better delay disease progression (score=2.71) and drugs with fewer side effects (score=2.39).

Input from KCC also provided information on issues patients face due to drug resistance. Antiangiogenic agents directed against the VEGF protein or the VEGF receptor is a central basis of current treatments, however eventual resistance to these agents is almost certain in advanced RCC. KCC stated that sequential treatments with existing available second-line therapies have some effect in addressing drug resistance, but additional more effective treatment options with better long-term disease control are desperately sought after by patients.

KCC acknowledged new immunotherapy drugs which represent an important breakthrough in cancer treatment as these therapies (eg., nivolumab) have proven to significantly improve overall survival. Despite this, the survival benefit from immunotherapy is not realized in the majority of kidney cancer patients and some patients find the treatment causes unexpected and sometimes serious side effects, unlike the side effects typically seen with more established/familiar treatments.

Recognizing that these immunotherapy agents are quite new, KCC indicated that patients would benefit strongly from more research that helps patients and clinicians to better:

- recognize side effects before they become serious
- identify patients who are likely to be at risk to potentially serious immune-mediated reactions
- Determine how side-effects can be treated and managed.

KCC indicated that should patients and their physicians, determine that immunotherapy is not suitable, it is critical that patients have more treatment options than currently available.

As part of a survey, patients and caregivers were asked: “If a new treatment was demonstrated to have overall effectiveness in treating RCC, including effectiveness on bone metastases, how important do you think it would be for that treatment to be made available to patients?” Patients were asked to rate this on a scale of 1 to 5 with 1 being "not important" and 5 being "very important". Results from 170 patients are in the table below:

1 (not important)	2	3	4	5 (very Important)	Weighted Average (WA)
0.0% (n=0)	0.59% (n=1)	2.94% (n=5)	4.12% (n=7)	92.35% (n=157)	4.88

The weighted average of patients' and caregivers' responses was 4.88, indicating overwhelmingly that they believe any new treatment demonstrating overall effectiveness in treating RCC, including effectiveness on bone metastases, needs to be available to patients. KCC indicated that access to new effective second- and third-line treatment alternatives is critical for patients to have the opportunity to halt disease progression, control drug resistance, overcome drug resistance mechanisms, and delay or prevent skeletal complications. With more treatment options, patients and oncologists can better individualize treatment plans according to specific disease/treatment history and contraindications, leading to the best possible outcomes and quality of life for the patient.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Cabozantinib

At the time of the submission for the previous pCODR review for cabozantinib for RCC, KCC indicated that experience with cabozantinib was rare in Canada as it had not yet received marketing approval, though it had received priority review status at Health Canada to expedite the regulatory approval process. For the METEOR trial which began in 2013, there were 40 patients enrolled at 11 sites in Canada with 23 patients in the cabozantinib arm. To better understand patient experience with this treatment, KCC collected information from patients outside of Canada. The survey collected information from 13 patients with experience using cabozantinib, including patients from Alberta (n=2), Ontario (n=2), Saskatchewan (n=1), U.S. (n=4), UK (n=3) and Republic of Ireland (n=1).

All patients report using cabozantinib as a single agent therapy. The patients report gaining access to the drug in various ways: two Canadian patients reported access through the METEOR trial, one patient in Western Canada indicated receiving provincial reimbursement for the drug, the three UK patients reported access through NHS, and the four U.S. patients reported access through private insurance. Patients/caregivers were asked the following questions:

Question #1: "Based on personal experience with cabozantinib, how would you rate its effectiveness in controlling your kidney cancer? 1 is "not effective" and 5 is "extremely effective"".

1 not effective	2	3	4	5 extremely effective	Total	Weighted Average (WA)
0.0% (n=0)	15.4% (n=2)	23.1% (n=3)	38.5% (n=5)	23.1% (n=3)	13	3.69

Question #2: "Prior to starting cabozantinib, had your cancer developed resistance to any other drugs for the treatment of RCC (had another drug you were taking ceased being effective)?"

Question #3: "In general, how would you rate the side effects of cabozantinib, with 1 being "completely intolerable" and 5 being "very tolerable.""

1 Completely intolerable	2	3	4	5 Very tolerable	Total	Weighted Average (WA)
7.7% (n=1)	23.1% (n=3)	38.5% (n=5)	30.8% (n=4)	0% (n=0)	13	**2.92**

Question #4: "On a scale of 1-5 how would you rate your quality of life (QoL) while taking cabozantinib? 1 is "Low Quality of Life", and 5 is "High Quality of Life.""

1 Low QoL	2	3	4	5 High QoL	Total	Weighted Average (WA)
15.4% (n=2)	7.7% (n=1)	30.8% (n=4)	46.2% (n=6)	0% (n=0)	13	**3.08**

Overall, patients and caregivers had fairly moderate thoughts regarding cabozantinib. Patients considered cabozantinib to be fairly effective (WA=3.69); none of the patients reported that cabozantinib was not effective at all. Respondents indicated a weighted average score of 3.08 regarding the impact of cabozantinib on quality of life; most patients reported a score of '3' or '4'. While none of the patients indicated the quality of life with cabozantinib being high (a score of '5'), two patients did report a very low quality of life (score of '1'). Most patients reported a score between '2' and '4' in regards to the tolerability of cabozantinib; none of the patients thought cabozantinib was very tolerable, however one pateints did indicate cabozantinib s being completely intolerable (score of '1').

When asked about whether they experienced drug resistance (Question #2 above), eleven patients responded with 10 reporting they had developed resistance to one or more pervious therapies. Highlighting KCC's previous statements regarding the intolerance after first-line treatment, all 13 patients with cabozantinib experience reported being previously treated with at least one other drug, these included sunitinib (n=10), temsirolimus (n=2), axitinib (n=2), everolimus (n=3), pazopanib (n=5), sorafenib (n=1), nivolumab (n=6), HD-IL2 (n=2). When rating the side effects of previous treatments (with 1 being "completely intolerable" and 5 being "very tolerable"), the weighted average was 2.92, identical to the weighted average of their rating of tolerability with cabozantinib (albeit with a different rating distribution).

Patients were asked to describe the side effects they experienced from taking cabozantinib that were particularly difficult to tolerate. Ten patients reported experiencing the following side effects:

- Diarrhea
- Hand foot syndrome and mouth sores
- Sore mouth
- Fatigue, loss of appetite and mouth sores
- weight loss and fatigue and general body health made us have the need to stop this therapy
- Hand, foot and mouth syndrome, overall swelling, fatigue
- Still very early in the treatment (only two weeks.) So far the side effects have been some fatigue and moderate increase in BP.
- Loss of appetite, fatigue
- Diarrhea, high liver numbers
- Diarrhea, occasional dehydration

The patients in this survey who had experience with cabozantinib report the tolerability and quality of life related to experienced side-effects as generally consistent with the patient-rated tolerability of other drugs used to treat mRCC (See section 3.1.2). KCC posited that opinions from their surveys confirm the results of the METEOR trial that also shows adverse events with cabozantinib as being similar to those expected with VEGF receptor inhibitor for the treatment of advanced RCC. It is the opinion of KCC that clinicians and patients have a decade of experience dealing with adverse events related to VEGF receptor inhibitor, and consider the benefits of improved overall survival related to cabozantinib to strongly outweigh the inconvenience of these adverse events.

Patients and caregivers were asked the following question related to the metastases of their disease: "When you started taking cabozantinib, were you aware of any spread of cancer to your bones?" Four (4) respondents indicated being aware of metastasis of cancer to the bones.

These 4 patients/caregivers were then asked:

1a. "If you were aware of the spread of cancer to your bones, did you have any associated complications such as fractures, spinal cord compression, bone pain, or hypercalcemia (where the calcium level in your blood is above normal -- weakening your bones)?" All four respondents answered "yes".

1b. "If you were aware of the spread of cancer to your bones, were you aware of any positive effect that cabozantinib may have had on the following? (check all that apply)."

Answer Choices	**Responses**
Incidence of fractures	0
Spinal cord compression	0
Hypercalcemia	1
Bone pain	0
Improved bone scans	2
Other	1

As stated by KCC, patients with experience with cabozantinib experience and who developed resistance to a previous treatment reported cabozantinib as effective, in most cases, in controlling their cancer. A sub population of patients that had cancer spread to their bones, report the drug has a positive effect on that site of metastases. KCC emphasized multiple times that patients and clinicians require greater treatment options for advanced RCC; based on the effectiveness of cabozantinib and the intolerance patients experience following their first treatment, KCC considers the addition of cabozantinib for the treatment of RCC to be beneficial.

KCC asked patients with experience using cabozantinib how it changed, or how it is expected to change, their long-term health and well-being? Ten Patients provided responses, with many indicating a positive impact on tumour shrinkage and greater stability of metastases:

- *Tumours and Mets have shrunk or remained stable since I began taking the drug.*
- *Secondary to maxilla/sinus which was removed twice by surgery is hoped to be held at bay by Cabo and all secondaries continue to shrink*
- *I am hoping it shrinks the tumour in my kidney and lymph nodes to go ahead with operation to remove*
- *Latest scan shows shrinkage in all metastasis sites and kidney tumour*

- *the ability to gain back the weight loss did not happen after this drug*
- *I feel that cabo is giving me another chance to live longer with RCC and mets.*
- *Always hoping for a complete response but only a few weeks into treatment with this new drug. But clinical trial indicate improved results with Cabo.*
- *Make mets stable*
- *Extended life. Less or no spread hopefully of metastasis*
- *Kept the tumor growth to a slow rate. 2 and a half years before the tumors reached 20% growth. Other than the diarrhea, the side effects were tolerable.*

Respondents were also asked to provide any additional information they thought pertinent to sharing about cabozantinib. Five respondents provided statements, many of which comments regarding side effects due to cabozantinib:

- *Its effective on a lower dose and side effects are less severe on a lower dose*
- *even though it was working well, the quality of life for the patient was intolerable due to the side affects*
- *I took 60 mg cabo for three 15 day cycles and ended up in the hospital due to side effects. My cancer grew rapidly in the 4 weeks I stopped taking the cabo with new mets showing up. I started taking 40 mg cabo now on my 2nd cycle and I'm doing better with side effects being a lot milder and it seems the cancer growth has slowed down or is getting stable. Scans this coming week will show results.*
- *Receiving the drug on "compassionate" use program. Not yet approved in Canada but it should be as it is currently approved in the US, Europe, and UK.*
- *We had bad interaction with Bactrim for an infection while on Cabo. Had to take a break from Cabo. For infection to clear.*

Finally, KCC asked respondents, "Can you tell us about your story and why access to cabozantinib and other therapies is so important to you?" Ten patients/caregivers provided comments/stories:

- *I was diagnosed with metastatic kidney cancer in Feb 2014. First line treatment was Sutent but it was intolerable due to side effects. I began a clinical trial Oct 2014 on Everilimous that was successful for 10 months before tumours were noted in my liver. Got put on Nivolamab following this and while there were virtually no side effects the tumours continued to grow on it. Next was pazopanib last Oct. Unfortunately I had a bad skin reaction to this drug and only lasted a month or two. I've been on Cabozantinib now since January and have had the best results to date, including necrosis of liver tumours and shrinkage of lymph nodes.*
- *Mets to maxilla/sinus area, lungs, hilar lymph nodes, glands and pancreas mean drugs are a lifeline. Paz worked for 4 1/2 years and Axitinib for a year. Cabozantinib have reduced all current secondaries in the first 3 months even on a reduced dose giving hope for long term survival*
- *If it wasn't for Sutent which worked for 9 months and now Cabo I'm sure I could be dead by now so it's very important to have these meds available. I'm lucky to have double insurance through my own work as well as through my spouse so we haven't had to pay anything for any of the therapies I've been on. I was diagnosed in 2008 and had 14 lb kidney tumor removed. Was diagnosed with mets in 2014. Sutent worked for the first 9 months, then nothing worked until I was put on Cabo a couple months ago. I had many radiations after Sutent stopped working due to mets to my brain, lung, humerus, pelvis, skin, arm, lymphnodes, T8, T11, adrenal gland, kidney, femoral. But I'm not giving up fighting now that cabo is giving me a chance to live a bit longer then expected!*

- *My husband died in April 2016 after eight years with known kidney cancer. The availability of a number of drugs was very important as he developed resistance to some and others just did not work for him. Without access to these drugs, or if access had been limited to one or two, he would not have survived as long as he did.*
- *My husband's kidney cancer is progressing and he is looking for the best possible option for complete response, tumor regression, and stability. He responds to TKI's so Cabo appears to be the top option.*
- *Stage 4 mccrcc. No treatment has worked in one year. Sutent failed, Nivolumab failed. Cancer spread considerably and he was given 6 mo. To live, as of today the cancer.*

3.3 Additional Information

No additional information was noted.

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:

- Axitinib and nivolumab are the current standard of care in second line treatment, and if axitinib is used as a second-line treatment, nivolumab is available as a third line treatment if patient remains good performance status
- Place in therapy and sequencing with currently available treatments and upcoming treatments
- Definition of treatment until patient no longer benefits and clarity on discontinuation criteria

Economic factors:

- Cost effectiveness compared to axitinib and nivolumab as second line therapies and cost effectiveness in the clinical setting where nivolumab is third line treatment
- Unknown and potentially long duration of therapy

Please see below for more details.

4.1 Factors Related to Comparators

Currently funded treatments in second line treatment of advanced or metastatic renal cell carcinoma include axitinib, everolimus and nivolumab. PAG noted at the time of the trial starting, everolimus would have been the appropriate comparator. However, axitinib and nivolumab would be the more appropriate comparator now. PAG noted that axitinib and nivolumab are funded choices in the second line setting in almost all provinces and are the current standard of care. Thus, information comparing cabozantinib to axitinib or nivolumab would be helpful for implementation, if cabozantinib is recommended. In some provinces, nivolumab is funded after one or two prior TKIs. PAG is seeking guidance on the sequencing of nivolumab after cabozantinib, if cabozantinib is chosen as a second line TKI option over axitinib. In provinces where everolimus, axitinib and nivolumab are not funded, data comparing cabozantinib to sorafenib would be an enabler to implementation in those provinces.

PAG also noted that nivolumab plus ipilimumab as well as lenvatinib plus everolimus are being reviewed at pCODR for renal cell carcinoma. PAG is seeking guidance on the place in therapy for cabozantinib and which patient population would benefit most from the therapy and which patient population would be best suited for treatment with other available therapies.

4.2 Factors Related to Patient Population

PAG noted that the funding request does not specify the number of previous treatments or the types of previous treatment. The majority of patients in the METEOR trial were treated with

sunitinib in first-line. PAG is seeking guidance on the use of cabozantinib in patients who were previously treated with more than one line of therapy and in patients previously treated with immunotherapy. In addition, although treatment with mTOR inhibitors (everolimus and temsirolimus) is not common, these may be used in some patients. PAG is seeking information on whether patients previously treated with mTOR inhibitors or in further lines of therapy (e.g., after third line or after everolimus) would be eligible for cabozantinib.

PAG noted that the funding request does not specify the histologic type of renal cell carcinoma. PAG noted that the METEOR trial enrolled only patients with clear cell histology. PAG is seeking clarity on the patient population who would be eligible for treatment with cabozantinib.

PAG has noted that the CABOSUN trial (randomized Phase II) for first-line use has been published and may be a reason for 'indication creep' for clinicians who want to use cabozantinib as first line in previously untreated patients. PAG recognizes that a review of the first-line indication is out of scope for this review, however, PAG would appreciate a guidance as to whether patients who have a documented intolerance to one or both sunitinib or pazopanib (funded first line TKI's) without disease progression should be eligible for cabozantinib funding.

PAG noted that patients were eligible for the METEOR trial if they received one or more prior VEGF therapies and is seeking guidance and data on the appropriate use and patient eligibility for cabozantinib in the following clinical situations:

- Patients who received sunitinib/pazopanib first line and then axitinib second line. Would cabozantinib be a third line option after 2 prior TKI's with patients remaining eligible nivolumab in the 4th line setting? Would cabozantinib be a 3rd line option after 2 prior TKI's for patients who are not candidates for nivolumab?
- Patients intolerant to everolimus but do not have disease progression on second line everolimus
- Patients who have started second-line treatment with everolimus but wish to switch to cabozantinib prior to disease progression
- Patients who have disease progression with nivolumab – i.e. third or fourth line use of cabozantinib (note: currently, other TKI's are not allowed following nivolumab failure)
- Patients who have recently failed everolimus or temsirolimus, and who are not candidates for nivolumab, as the METEOR trial did not enroll patients with previous mTOR inhibitor therapy
- Patients using second line everolimus or axitinib who have not progressed and who have a preference to switch to cabozantinib due to the results from the METEOR trial.

4.3 Factors Related to Dosing

Funding request is for treatment until patient no longer has clinical benefit. PAG is seeking clarity on this statement and how it will affect treatment duration and criteria for treatment discontinuation.

PAG noted that there are 20 mg, 40 mg and 60 mg tablets available and may be easier for dose reductions. Dose adjustment can be accomplished by changing the tablet strength dispensed (note: this may increase drug wastage of previously dispensed tablets of a higher strength) or by adjusting the number of tablets to take if the lower strength is dispensed (note: this reduces potential for drug wastage, but may not be an option depending on the pricing). PAG is seeking information on the dose intensity and the frequency of dose adjustments.

4.4 Factors Related to Implementation Costs

As cabozantinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation.

4.5 Factors Related to Health System

PAG noted that the toxicity profile and side effects of TKIs are well known by physicians, nurses and pharmacists who treat renal cell carcinoma as other TKIs are in that space. This would be an enabler to implementation.

Cabozantinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

At the time of the PAG input, the price of cabozantinib was not available. PAG is seeking information on the cost and noted that flat pricing of all tablet strengths is more costly for patients who are dispensed the lower strengths and adjusting dose by adjusting the number of tablets.

PAG noted that CABOSUN trial for first line treatment with cabozantinib is published and was referenced in the presubmission information for this review. However, the funding request is for previously treated patients. PAG is seeking information on if and when a submission for first line use would be submitted to Health Canada and to pCODR.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided for cabozantinib for the treatment of patients with advanced RCC who have received prior therapy. Input was provided as a joint submission with two clinicians and a pharmacist, who will be referred to as the health professionals throughout the summary. Their input is summarized below.

The health professionals identified cabozantinib as being provided to patients as a second- or further line of therapy. The improvements in PFS and OS, regardless of the fact that some patients had multiple lines of previous therapy in the METEOR trial, was highlighted. However, the toxicity of cabozantinib was noted as a potential challenge, and was mentioned to be comparable to other TKI therapies. While cabozantinib has not been compared to treatments, such as nivolumab or axitinib, the clinician input did suggest the superiority of cabozantinib over everolimus.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for Renal Cell Carcinoma

The health professionals stated that in patients with mRCC who received at least one line of anti-VEGF therapy, cabazitaxel showed a survival improvement. In the clinician's jurisdiction, standard first-line treatment is a TKI, such as pazopanib or sunitinib, with nivolumab or axitinib as ulterior line therapy. The health professionals stated that everolimus, which has shown to be inferior to both nivolumab and cabozantinib, is rarely used any more.

5.2 Eligible Patient Population

As the patients targeted for this indication have advanced disease, the health professionals estimated very little prevalent population. The health professionals estimated the incidence of patients who may use cabozantinib as second- or third-line therapy to be approximately one third of patients who receive a TKI as first-line therapy.

5.3 Identify Key Benefits and Harms with Cabozantinib

The health professionals identified the clear improvements in survival and in response rates as advantages of cabozantinib. The potential toxicity was listed as the main challenge related to cabozantinib, which was stated to be comparable to toxicity profiles seen with previous TKI therapies. The health professionals noted that patients who were excluded from the METEOR study are not likely to receive cabozantinib.

5.4 Advantages of Cabozantinib Over Current Treatments

While cabozantinib has not been compared to axitinib or nivolumab, which are options as post first-line TKI therapies, the health professionals emphasized the superiority of cabozantinib over everolimus. PFS and OS were noteworthy of patients in the METEOR trial, even among patients who could have received three or more lines of therapy. Although the health professionals identified an unmet need for patients who are in second-line therapy, they agreed that cabozantinib should not be limited to only second-line patients as this would refer to only 5% of patients in the METEOR study.

5.5 Sequencing and Priority of Treatments with Cabozantinib

In the health professionals' opinion, cabozantinib would be placed after first-line TKI therapy. Based on the population and results of the METEOR trial, cabozantinib could also be given after

axitinib or nivolumab. It was stated cabozantinib would replace everolimus, which is now rarely used based on the known superiority of nivolumab over everolimus.

5.6 Companion Diagnostic Testing

N/A

5.7 Additional Information

The clinician input stated that the pCODR clinician input feedback process currently does not allow for pharmacists to register and provide input/feedback. The input recommended that pCODR amend this process to consider the opinions of pharmacists in addition to clinicians to provide greater insight into local practices and identify areas of unmet need.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of cabozantinib in adult patients with advanced renal cell carcinoma (RCC) who have received prior therapy.

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 are outlined in section 7 and section 8.

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 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of cabozantinib should be included.
	Adult patients with advanced RCC who have received prior VEGF-targeted therapy
	
	Subgroups:
	• ECOG (0 vs. 1)
	• Smoking status (Current vs. former vs. never)
	• Number of previous VEGFR TKIs (1 vs. ≥2)
	• Duration of first VEGFR TKI (≤6 months vs. >6 months)
	• Progression after start of most recent VEGFR TKI (≤3 months vs. >3 months)
	• Previous systemic therapy
	  ○ Sunitinib
	  ○ Pazopanib
	  ○ Axitinib
	  ○ Nivolumab
	  ○ Ipilimumab & nivolumab
		Cabozantinib	Oral targeted therapies
			• Axitinib
			• Pazopanib
			
			mTOR inhibitors
			• Everolimus
			• Levatinib and Everolimus
			
			Immunotherapies
			• Nivolumab
				Primary
				• OS
				• PFS
				• HRQoL
				
				Secondary
				• ORR
				• DOR
				• DCR
				
				Safety
				• AEs
				• SAEs
				• WDAEs
				• AEs Special Interests (cardiac safety, thyroid)

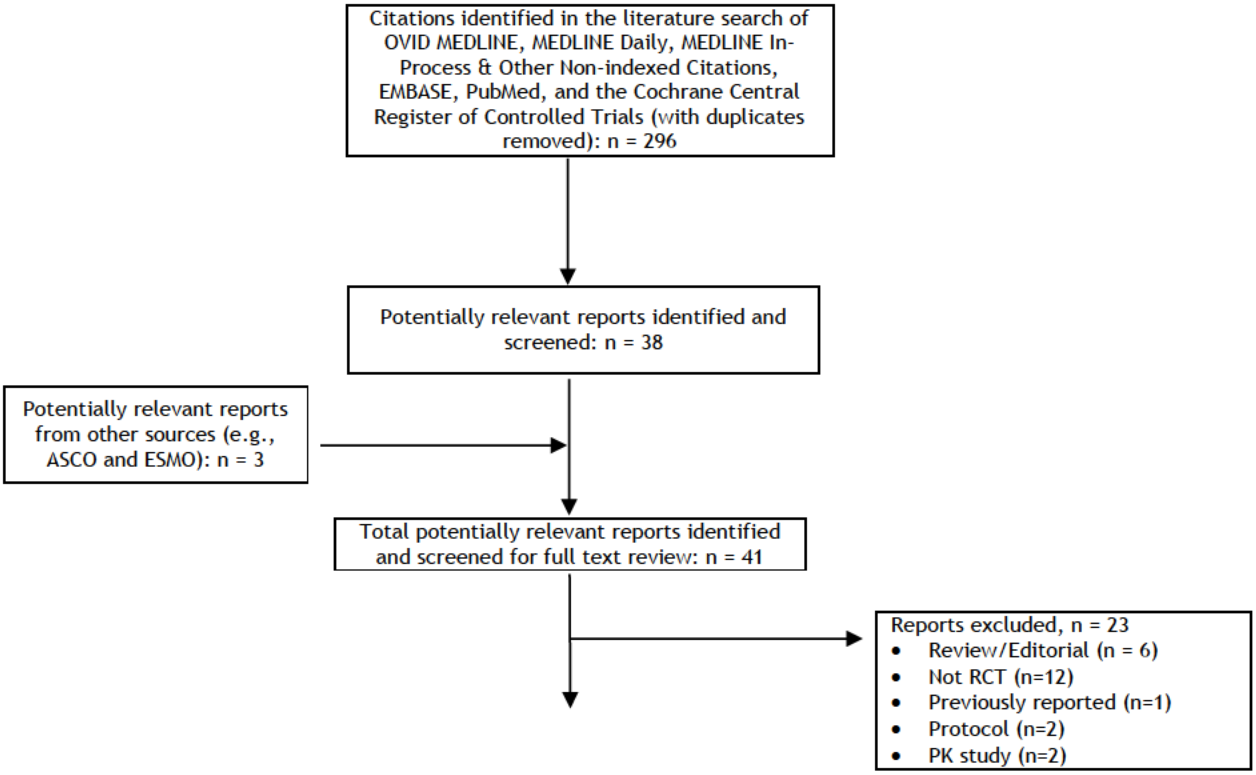
Abbreviations: RCC = renal cell carcinoma; HRQoL=Health related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response; ORR = overall response rate				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 296 potentially relevant reports identified, one study (METEOR), reported in 18 citations, was included in the pCODR systematic review (Figure 1).[1,2,5,6,29-41] Twenty-three reports were excluded because six were reviews, 12 were not RCTs, two were protocols and two were pharmacokinetic studies. Additional reports related to the METEOR trial were obtained from the Submitter.[3,4,7]

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



18 reports presenting data from 1 clinical trials

Study (15)

Amzal et al (2017)[29]	Cella et al (2018)[6]	Choueiri et al (2015)[1]	Choueiri et al (2016)[2]	Donskov et al (2017)[30]
Escudier et al (2018)[32]	Grande et al (2018)[31]	Heng et al (2017)[33]	Hessel et al (2016)[42]	Motzer et al (2018)[34]
Pal et al (2017)[35]	Powles et al (2017)[36]	Powles et al (2018)[37]	Schmidinger et al (2017)[38]	Tannir et al (2016)[39]

Reports identified and included from other sources:

Clinicaltrials.gov[40]	EMA[5]	NICE[41]

Note: Additional data related to the METEOR were also obtained through requests to the Submitter by pCODR [Checkpoint Responses[7], Clinical Summary[4], METEOR Study Protocol[3], NMA[4]]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

a) Trial

The pCODR systematic review included one phase 3 RCT that assessed the safety and efficacy of cabozantinib in patients with advanced RCC who progressed after previous VEGFR TKI treatment (METEOR; N = 658).[1,2] The summary and quality characteristics of the METEOR trial are presented in Table 4 and Table 5.

Table 4: Summary of the METEOR Trial Characteristics

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
METEOR Trial **Other identifiers** NCT01865747 **Characteristics** Global, multicentre, open-label, randomized phase 3 study **Sample size** Randomized: 658 Treated: 653 **Locations** **Start date:** 08/2013 to 11/2014 **Interim analysis cut-off** 22-May-2015 **Unplanned interim analysis cut-off** 31-Dec-2015 02-Oct-2016 **Funding** Exelixis	<u>Key Inclusion Criteria:</u> • Aged 18 years and older • Documented histological or cytological diagnosis of advanced or metastatic RCC with a clear cell component. • Measurable disease per RECIST as assessed by the investigator. • KPS score of ≥ 70% and adequate organ function • Must have received at least one VEGFR-targeting TKI (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib). • For the most recently received VEGFR-targeting TKI the following criteria must apply: a) Must have radiographically progressed during treatment, or been treated for at least 4 weeks and radiographically progressed within 6 months after the last dose. Radiographic progression is defined as unequivocal progression of existing tumor lesions or developing new tumor lesions as assessed by the investigator on CT or MRI scans. b) The last dose must have been within 6 months before the date of randomization. • Recovery from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. • Adequate organ and marrow function. <u>Key Exclusion Criteria:</u> • Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (eg, temsirolimus), or cabozantinib. • Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization. • Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before randomization. • Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomization. Systemic treatment with radionuclides within 6 weeks before randomization. Subjects with clinically	Cabozantinib (60mg/d) Everolimus (10mg/d)	<u>Primary</u> **PFS** <u>Secondary</u> **OS** **ORR** **Tertiary** **DOR** **HRQoL** **Safety**

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	relevant ongoing complications from prior radiation therapy are not eligible. • Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before randomization. • Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors. • Chronic treatment with corticosteroids or other immunosuppressive agents. • Serious illness other than cancer. • Major surgery within 3 months before randomization. Complete wound healing from major surgery must have occurred 1 month before randomization and from minor surgery at least 10 days before randomization. • Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low grade tumors. • Uncontrolled hypertension or clinically significant cardiovascular, gastrointestinal, wound healing, or infectious comorbidities.		

Abbreviation: RCC = renal cell cancer; KPS = Karnofsky Performance Status; PFS = progression free survival; OS = overall survival; ORR = overall response rate; DOR = duration of response; HRQoL = health related quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine kinase inhibitor; CT = computed tomography; MRI = magnetic resonance imaging; AE = adverse events

Table 5: Select quality characteristics of the METEOR trial

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Interim analysis	Final analysis	Crossover
METEOR	Cabozanitinb AND Everolimus	PFS	650[A]	658	IVRS, stratified[B]	Yes	Open-label[C]	Yes	Yes	No[D]	No

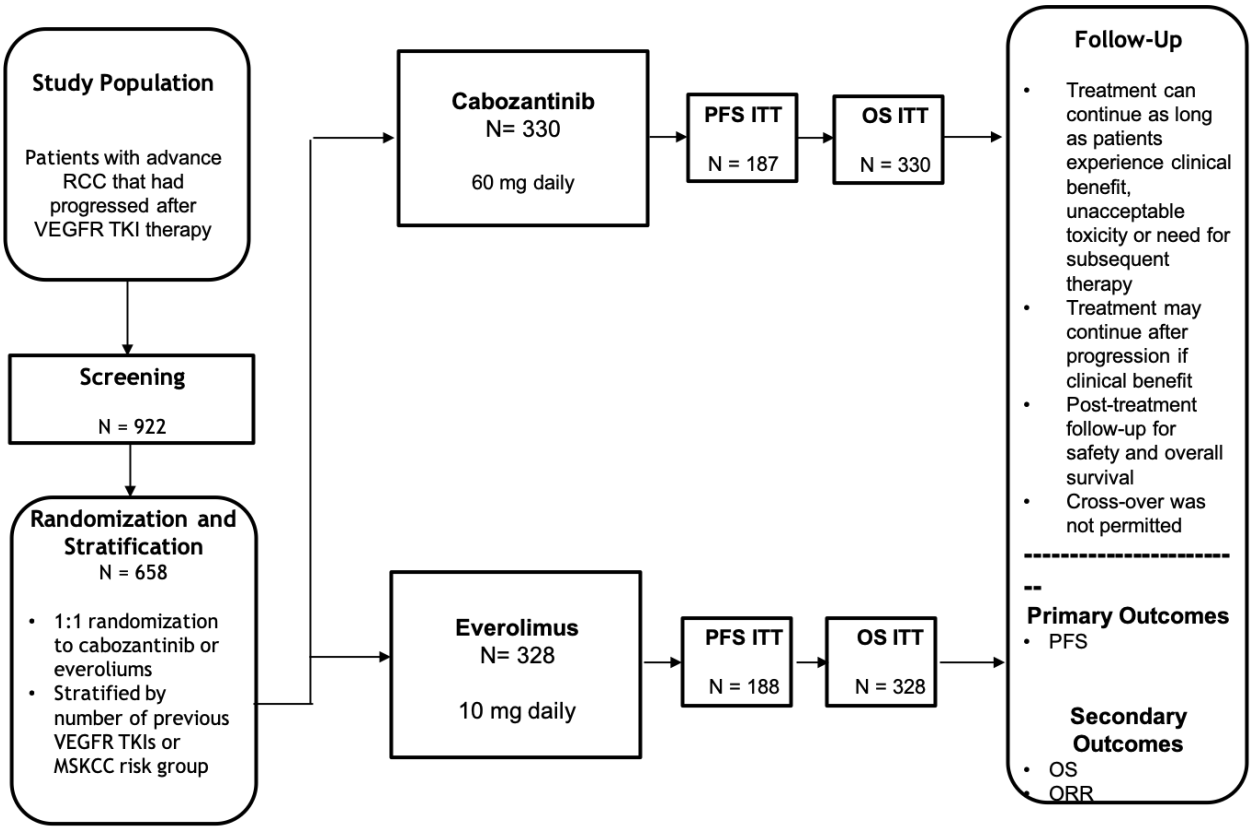
[A] A power calculation was provided for both PFS and OS. For PFS, 259 events (i.e. disease progression or death) were required to have 90% to detect a HR of 0.667 using a log-rank test and a two-sided alpha of 0.05. For OS, 259 events (i.e. disease progression or death) were required to have 90% to detect a HR of 0.667 using a log-rank test and a two-sided alpha of 0.05.[3]
[B] Randomization was stratified by number of prior VEGFR-targeting TKI therapies (1 vs. 2 or more) and MSKCC risk group (favourable, intermediate or poor).
[C] Investigators and patients were not blinded to treatment assignment. Disease progression was assessed by a BIRC.
[D] At the time of the primary analysis the stopping boundaries were not met for OS. Thus, the Manufacturer conducted an unplanned interim analysis at 31-Dec-2015, which represents a minimum of 13 months follow-up.[41] The trial is ongoing.

Trial Design

The METEOR trial is a large, multicentre, open-label, phase 3 RCT. Six hundred and fifty-eight patients were enrolled at 173 sites in 25 countries including 40 patients at 11 sites in Canada.[5] The aim of the METEOR trial was to assess the effect of cabozantinib in comparison to everolimus in

patients with advance RCC that had progressed after VEGFR TKI therapy. This study was funded by Exelixis. The eligibility criteria of the METEOR trial is outlined in Table 4.

Figure 2: Study Design of the METEOR Trial



Abbreviations: RCC = renal cell carcinoma; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; TKI = tyrosine kinase inhibitor; MSKCC = Memorial Sloan-Kettering Cancer Center ; ITT = intention-to-treat

Figure 2 represents the study design of the METEOR trial. The METEOR trial consisted of three phases: the treatment phase, the maintenance phase and the follow-up phase.[3] These phases will be described in further detail, more specifically:

Treatment Phase[3]

- Eligible patients were randomized a using a computerized interactive voice and web response system.
- Patients were randomized on a 1:1 ratio to receive either cabozantinib or everolimus.
- Randomization was stratified by the number of prior VEGFR-targeting TKI therapies (1 vs. 2 or more) and MSKCC risk group (favourable, intermediate or poor). Randomization was performed using stratified permuted blocks.
- Radiological assessments by CT or MRI were performed at baseline and every 8 weeks for the first 12 months and then every 12 weeks thereafter. Tumour progression was assessed using RECIST 1.1 by BIRC.
- Patients were followed by for survival every 8 weeks.
- Patients received study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer treatment, or until any other reasons for treatment discontinuation.

- Patients who progressed per RECIST1.1 could still continue treatment if the investigator believed that the patient would receive clinical benefit.
- Cross-over was not permitted.

Maintenance Phase[3]

- Patients who were still continuing therapy entered the Maintenance Phase when sufficient data had been collected on all study outcomes.
- Patients continued to receive their assigned therapy until they met the prespecified criteria for study discontinuation.

Follow-Up Phase[3]

- After discontinuation, patients were follow-up for overall survival and adverse events (AEs).
- HRQoL and radiological tumour assessments were collected, regardless of dose discontinuation, until the later of 8 weeks after radiographic progression per RECIST 1.1 as determined by the investigator, or the date of the decision to permanently discontinue study treatment.

Statistical Analysis

Power Calculation and Sample Size: The METEOR trial was designed to provide adequate power for the assessment of both progression-free survival (PFS) and OS. For PFS, 259 events (disease progression or death) were required to provide 90% power to detect a hazard ratio (HR) of 0.667 (7.4 months with cabozantinib vs. 5 months with everolimus), using the log-rank test and two-sided significance of 0.05. [3] For OS, a single interim analysis at the time of the primary endpoint (i.e., PFS) analysis and a subsequent final analysis was assumed.[3] Four hundred and eight deaths were required to provide 80% power to detect a HR of 0.75 (20 months with cabozantinib vs. 15 months with everolimus) for OS, using the log-rank test and two sided significance level of 0.04.[3] The authours estimated that a sample size of 375 patients would be adequate for the PFS analysis but they noted that a larger sample size would be required to provide sufficient power for the OS analysis.[3] The authours designed to trial so the primary analysis would be conducted when 259 PFS events had occurred in 375 patients and 650 patients had been enrolled in the trial. The rationale for using this statistical analysis was to allow for a longer follow-up period in order not to bias the PFS estimates toward patients who experience early progression.[3]

Interim Analyses: The trial was designed to conduct one interim analysis on 22-May-2015. However, at this time point, OS was immature, and therefore, the Manufacturer conducted an unplanned interim analysis at 31-Dec-2015, which represents a minimum of 13 months follow-up.[41] An updated analysis of OS was conducted on 2-October-2016 but the results of this analysis have not been published. [34]

Analysis Set: Efficacy was evaluated in two populations according to the ITT principle. The safety population was composed of all patients who received any amount of study treatment and according to the treatment they received.[3]

Endpoints: The primary outcome in the trial was PFS and the secondary outcomes included: OS and overall response rate (ORR). Tertiary outcomes included: duration of response (DOR), health related quality of life (HRQoL) and safety.

Multiplicity: The NICE Report stated that multiplicity was accounted for in the METEOR trial by using a fixed-sequence testing procedure, a modified Bonferroni correction, which divided the alpha between the secondary endpoints, and an alpha spending function.[41]

Missing data: The protocol stated that missing data will not be imputed and missing data will be treated as missing.[3]

Protocol Amendments

One global protocol amendment was made on 17-Apr-2014.[5] These changes included: adding a maintenance period to the treatment period when sufficient data had been collected; limiting the study population to include 10% of patients had had received antibodies targeting the programmed cell death immune receptor, PD-1, or its ligands, PD-L1/L2; adding study endpoints (i.e. changes in bone scans and serum calcium from baseline) and further clarifications.[5] It was reported in EMA that the majority of patients had been enrolled in the trial when this amendment had been made (78% in cabozantinib and 75% in everolimus, respectively).[5]

Three changes were made to the statistical plan. The first change to the statistical plan occurred before the primary analysis and the other changes were made after the primary analysis.[5] EMA considered the changes to be minor.[5]

c) Populations

Baseline characteristics for patients enrolled in METEOR are presented in Table 6. The baseline characteristics appeared to be balanced across all treatment groups. Overall, the majority of patients were male (75%), white (81%), had an ECOG of 0 (67%) and a favourable (45.5%) or intermediate (41.5%) MSKCC status.[1] Additionally, 70.5% of patients had previously treated with one line of VEGFR TKIs and the majority had received sunitinib (63%) or pazopanib (42.5%).[1]

Table 6: Baseline characteristics of patients enrolled in METEOR

Table 22 - Demographic and Baseline Characteristics (ITT and PITT Populations) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Age (years)				
Median	62.5	62.0	62.0	61.0
(range)	(32, 86)	(31, 84)	(36, 83)	(31, 84)
< 65, n (%)	196 (59)	198 (60)	118 (63)	116 (62)
≥ 65, n (%)	134 (41)	130 (40)	69 (37)	72 (38)
65 to < 75, n (%)	107 (32)	94 (29)	56 (30)	54 (29)
75 to <85, n (%)	26 (7.9)	36 (11)	13 (7.0)	18 (9.6)
≥ 85, n (%)	1 (0.3)	0	0	0
Male, n (%)	253 (77)	241 (73)	142 (76)	130 (69)
Female, n (%)	77 (23)	86 (26)[a]	45 (24)	57 (30)[a]
White, n (%)	269 (82)	263 (80)	157 (84)	147 (78)
Asian, n (%)	21 (6.4)	26 (7.9)	12 (6.4)	20 (11)
Black/African American, n (%)	6 (1.8)	3 (0.9)	4 (2.1)	2 (1.1)
Other, n (%)	19 (5.8)	13 (4.0)	10 (5.3)	6 (3.2)
Not Reported, n (%)	15 (4.5)	22 (6.7)[a]	4 (2.1)	12 (6.4)[a]
North America, n (%)	118 (36)	122 (37)	76 (41)	64 (34)
Europe, n (%)	167 (51)	153 (47)	83 (44)	84 (45)
Asia Pacific, n (%)	39 (12)	47 (14)	25 (13)	36 (19)
Latin America, n (%)	6 (1.8)	6 (1.8)	3 (1.6)	4 (2.1)
Stratification factors (per CRF), n (%)				
Prior VEGFR-TKI = 1	235 (71)	229 (70)	137 (73)	136 (72)
Prior VEGFR-TKI ≥ 2	95 (29)	99 (30)	50 (27)	52 (28)
MSKCC risk factors = 0 (favorable) (Motzer et al 2004)[b]	150 (45)	150 (46)	80 (43)	83 (44)
MSKCC risk factors = 1 (intermediate)	139 (42)	135 (41)	80 (43)	75 (40)
MSKCC risk factors = 2 or 3 (poor)	41 (12)	43 (13)	27 (14)	30 (16)
Prior VEGFR-TKI = 1, MSKCC risk factors = 0	102 (31)	100 (30)	55 (29)	59 (31)
Prior VEGFR-TKI = 1, MSKCC risk factors = 1	107 (32)	103 (31)	64 (34)	58 (31)
Prior VEGFR-TKI = 1, MSKCC risk factors = 2 or 3	26 (7.9)	26 (7.9)	18 (9.6)	19 (10)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors =0	48 (15)	50 (15)	25 (13)	24 (13)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors = 1	32 (9.7)	32 (9.8)	16 (8.6)	17 (9.0)
Prior VEGFR-TKI ≥ 2 or more, MSKCC risk factors = 2 or 3	15 (4.5)	17 (5.2)	9 (4.8)	11 (5.9)
Heng Prognostic Criteria, n (%) (Heng et al 2009)[c]				
0 adverse factors (favorable risk)	66 (20)	62 (19)	38 (20)	33 (18)
1-2 adverse factors (intermediate risk)	210 (64)	214 (65)	114 (61)	120 (64)
3-6 adverse factors (poor risk)	54 (16)	52 (16)	35 (19)	35 (19)
Karnofsky Performance Status, n (%)[d]				
70	29 (8.8)	22 (6.7)	15 (8.0)	16 (8.5)
≥ 80	301 (91)	306 (93)	172 (92)	172 (91)

Hgb, haemoglobin, (P)ITT, (Primary) endpoint intent-to-treat; IVRS/IWRS, interactive voice recognition/web response system; KPS, Karnofsky Performance Status; LLN (ULN), lower (upper) limit of normal; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a] In addition, gender and race for one subject in the everolimus arm were missing.

[b] KPS < 80%, Hgb < 13 g/dL for males and < 11.5 g/dL for females, corrected serum calcium > ULN

[c] Hemoglobin < LLN, corrected calcium > ULN, KPS < 80%, time from initial diagnosis to initiation of therapy of < 1 year, absolute neutrophil count > ULN, and platelets > ULN

[d] KPS (protocol-permitted scores): 100 (normal activity), 90 (normal activity, minor signs and symptoms), 80 (normal activity with effort, some signs and symptoms), 70 (unable to carry on normal activity or to work, cares for self)

Table 13 - Baseline Disease History and Baseline Status (ITT and PITT) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Diagnosis of RCC with a clear cell component by histology or cytology, n (%)	330 (100)	327 (100)[a]	187 (100)	187 (99)[a]
Time from initial histological/cytological diagnosis to randomization, n (%)				
< 1 year	59 (18)	76 (23)	34 (18)	44 (23)
≥ 1 year	271 (82)	251 (77)	153 (82)	143 (76)
Median (years)	2.8	2.5	2.6	2.4
Current Disease Stage, n (%)				
Stage IV	272 (82)	287 (88)	153 (82)	166 (88)
Stage III	34 (10)	24 (7.3)	20 (11)	13 (6.9)
Unknown	24 (7.3)	16 (4.9)	14 (7.5)	8 (4.3)
Extent of Baseline Disease by IRC, n (%)				
Bone (CT or MRI)	77 (23)	65 (20)	39 (21)	32 (17)
Visceral	241 (73)	245 (75)	139 (74)	142 (76)
Lung	204 (62)	212 (65)	115 (61)	126 (67)
Liver	88 (27)	103 (31)	52 (28)	58 (31)
Brain	2 (0.6)	1 (0.3)	2 (1.1)	1 (0.5)
Lymph Node	206 (62)	199 (61)	124 (66)	110 (59)
Kidney	70 (21)	66 (20)	46 (25)	36 (19)
Other	23 (7)	21 (6.4)	16 (8.6)	10 (5.3)
Number of Involved Organs by IRC, n (%)				
1	59 (18)	56 (17)	31 (17)	31 (16)
2	101 (31)	77 (23)	57 (30)	48 (26)
≥ 3	168 (51)	190 (58)	98 (52)	105 (56)
Missing	2 (0.6)	5 (1.5)	1 (0.5)	4 (2.1)
SoD (mm), median (range)	65.2 (0, 291)	65.0 (0, 258)	70.0 (0, 291)	77.0 (0, 231)
MET Immunohistochemistry Status[b], n (%)				
High	48 (15)	48 (15)	30 (16)	26 (14)
Low	138 (42)	151 (46)	83 (44)	90 (48)
Unknown	144 (44)	129 (39)	74 (40)	72 (38)

IRC, independent radiology committee; (P)ITT, (Primary) Intent to Treat; RCC, renal cell carcinoma; SoD, sum of lesion diameters

a One subject (Subject 4933 3382) had a diagnosis of undifferentiated RCC and is excluded from the numerator. For the other subject (Subject 1522 3098), the pathologist could not verify a clear cell histology because of limited tissue, but a clear cell histology was favoured; this subject is included in the numerator.

b Status of high and low based on cutoff of ≥ 50% of tumour tissue stained with an intensity of 2+ or 3+.

Table 24 - Prior Nephrectomy, Cancer, and Radiation Therapy (ITT and PITT) 22 May 2015

Subject Characteristic	ITT Population		PITT Population	
	Cabozantinib (N = 330)	Everolimus (N = 328)	Cabozantinib (N = 187)	Everolimus (N = 188)
Prior nephrectomy, n (%)	283 (86)	279 (85)	157 (84)	153 (81)
Prior systemic non-radiation treatment agents Median (range) per subject	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 6)	1.0 (1, 7)
Number of prior VEGFR-TKI agents per subject, n (%)				
1	235 (71)	229 (70)	137 (73)	136 (72)
2	84 (25)	91 (28)	42 (22)	49 (26)
≥ 3	11 (3.3)	8 (2.4)	8 (4.3)	3 (1.6)
Median (range) per subject	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 4)
Type of prior VEGFR-TKIs, n (%)				
Sunitinib	210 (64)	205 (63)	114 (61)	113 (60)
Pazopanib	144 (44)	136 (41)	87 (47)	78 (41)
Axitinib	52 (16)	55 (17)	28 (15)	28 (15)
Sorafenib	21 (6.4)	31 (9.5)	11 (5.9)	19 (10)
Other VEGFR-TKI	8 (2.4)	10 (3.0)	4 (2.1)	6 (3.2)
Selected prior systemic anti-cancer therapies (non VEGFR-TKI), n (%)				
Bevacizumab	5 (1.5)	11 (3.4)	1 (0.5)	7 (3.7)
Interleukin 2[a]	19 (5.8)	29 (8.8)	10 (5.3)	13 (6.9)
Interferon-α	19 (5.8)	23 (7.0)	6 (3.2)	12 (6.4)
Anti-PD-1/PD-L1/PD-L2 targeting agents	18 (5.5)	14 (4.3)	9 (4.8)	11 (5.9)
Nivolumab[b]	17 (5.2)	14 (4.3)	9 (4.8)	11 (5.9)
Atezolizumab/MDPL3280A[b]	1 (0.3)	0	0	0
First VEGFR-TKI treatment duration, n (%)				
≤ 6 months	88 (27)	102 (31)	54 (29)	62 (33)
> 6 months	242 (73)	224 (68)	133 (71)	126 (67)
Radiographic progression during treatment or within 6 months after last dose of most recent VEGFR-TKI therapy, n (%)	325 (98)	323 (98)	186 (99)	185 (98)
Median time from radiographic progression after most-recent VEGFR-TKI to randomization (months)	1.02	1.25	0.94	1.23
Median (range) types of prior radiation therapies per subject	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 4)	1.0 (1, 3)
Prior Radiation Therapies, n (%)	110 (33)	108 (33)	56 (30)	61 (32)
EBRT	106 (32)	105 (32)	53 (28)	58 (31)
Brachytherapy	6 (1.8)	4 (1.2)	4 (2.1)	3 (1.6)
Radioisotopes	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)

anti-PD-1, anti-programmed cell death immune receptor-1 or its ligands (PD-L1/PD-L2); EBRT, external beam radiation therapy; (P)ITT, (Primary) Intent to Treat; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

a Note in the post-text tables, interleukin-2 is cited as "interleukins"

b Enrollment of subjects previously treated with agents targeting PD-1 or its ligands (PD-L1/PD-L2) was limited to approximately 10% of the population (a maximum of approximately 65 subjects). Note in the post-text table, nivolumab is cited as "monoclonal antibodies" and atezolizumab is cited as an "investigational drug".

c Other types of EBRT were received by <10% of subjects in either treatment arm

Data Source: EMA Report[5]. Committee for Medicinal Products for Human Use. Assessment report: Cabometyx. *(European public assessment report)*. London (GB): European Medicines Agency; 2016 Jul 21. https://www.ema.europa.eu/documents/assessment-report/cabometyx-epar-public-assessment-report_en.pdf. Accessed 2019 Jan 03.

d) Interventions

Treatment Dosing Schedule

The dosing schedule for the two treatment arms in the METEOR trial are presented below[3]:

- Cabozantinib
  - Cabozantinib at an oral dose of 60 mg per day
    - Dose should be maintained in the absence of treatment-emergent toxicities
    - Patients received their first dose of cabozantinib in the clinic and subsequent treatment was self-administered at home

- Everolimus
    - Everolimus at an oral dose of 10 mg per day
        - Dose should be maintained in the absence of treatment-emergent toxicities
        - Patients received their first dose of everolimus in the clinic and subsequent treatment was self-administered at home

Dose delays, reductions or modifications

Dose delays, reductions and modifications for the two treatment arms in the METEOR trial are presented below[3]:

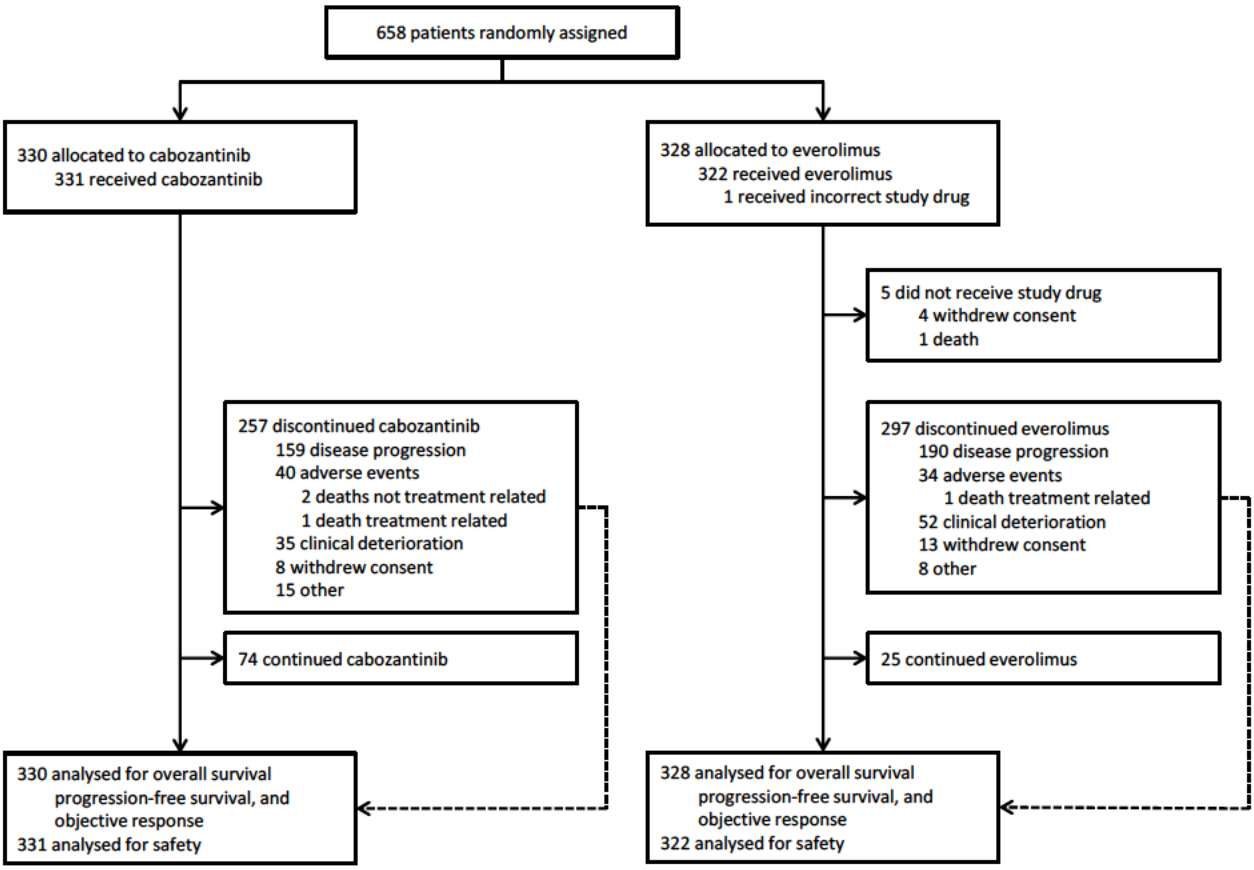
- Cabozantinib
    - Dose reductions were permitted for unacceptable toxicities. Two dose reductions of cabozantinib were permitted, which included a reduced dose of 40 mg/d followed by a dose of 20 mg/d. Cabozantinib was discontinued if patients could not tolerate the 20 mg/d oral dose.
    - Dose interruption were also permitted for AEs at any time during the trial. Patients were discontinued from the trial if the discontinuation lasted longer than 6 weeks.
    - Cabozantinib was reinstituted to the normal dose when a patient recovered from a non-treatment-related AE. However, the reinstituted dose could be reduced if the patient recovered from a treatment-related AE.
    - Dose reescalation was not permitted for a dose reduction caused by grade 4 hematologic toxicities or AEs affecting major organs.
- Everolimus
    - Dose reductions were permitted for unacceptable toxicities. The dose could be reduced to a 5 mg and then a 2.5 mg daily dose.
    - Dose interruption were also permitted for AEs at any time during the trial. Patients were discontinued from treatment if the discontinuation lasted longer than 6 weeks.

e) Patient Disposition

Patient disposition for the METEOR trial is summarized in Figure 3.[2] In total, there were 658 patients enrolled in the trial. Patients were randomized to receive either cabozantinib (N = 330) or everolimus (N=328). Six patients in the everolimus arm were not treated with their assigned therapies (Figure 3) because four patients withdrew consent, one patient died and one patient was incorrectly treated with cabozantinib.

At the later data cut-off of 31-Dec-2015, most patients had discontinued from their assigned therapies. [2] Choueiri et al (2016) reported that 22% of patients in the cabozantinib arm and 8% of patients in the everolimus arm remained on the study. [2] The most common reasons for termination in both treatment groups were: disease progression, adverse events and clinical deterioration.[2] Additionally, at the cut-off date of 02-October-2016, 11% of patients in the cabozantinib arm (N=36) and 2.5% of patients in the everolimus arm (N=8) remained on therapy. [34]

Figure 3: Patient disposition for the METEOR trial



Data Source: Choueiri et al (2016) Lancet Oncol[2] Reprinted from The Lancet Oncology, Vol. 17 number 7, Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, Page No. 920, Copyright (2016), with permission from Elsevier.

f) Limitations/Sources of Bias

- Overall, the METEOR trial was a well-designed trial and of good quality. However, a few aspects should be taken into consideration when interpreting the data, more specifically: The METEOR trial was an open label study. The open label design has the potential to bias outcomes, including the secondary endpoints, such as PFS, patient reported outcomes and safety. However, bias was minimised for the primary endpoint of PFS and secondary endpoint of ORR by evaluation of radiographic assessments by a masked central independent radiology review committee. Additionally, radiographic assessments were continued beyond investigator-determined progression to reduce missing data arising from discordance between the investigator and the independent radiology review committee about the date of progression.

- The METEOR trial assessed the effect of cabozantinib compared to everolimus. Other potentially relevant comparators were not assessed in this study (i.e. nivolumab, axitinib). Of note, the submitter provided a published network meta-analysis5 which includes other comparators such as everolimus, nivolumab and axitinib which will be critically appraised and assessed in the full review.

- Data pertaining to the secondary endpoint in the trial, OS, was immature at the prespecified interim analysis. An unplanned interim analysis was conducted at a later data cut-off date with a minimum of 13 months of follow-up. By conducting this unplanned interim analysis, the submitter may have increased the risk of type 1 error in the subsequent overall survival analysis. It is unknown at this time if the alpha was adjusted to account for multiple testing and for the additional unplanned interim analysis.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression-free survival

PFS was the primary outcome in the METEOR trial. It was defined as the time from randomization to disease progression as assessed by BIRC using RECIST 1.1 or death due to any cause.[3] Choueiri et al (2016) used Kaplan-Meier analyses to obtain the estimates of PFS for each treatment group with corresponding 95% confidence intervals (CIs). Differences in treatment effect were tested using a stratified log-rank p-value.[1] Stratified Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CIs.[1]

The 22-May-2015 data cut-off was used for the primary analysis of PFS, which represents a minimum of 11 months of follow-up for PFS and 6 months for OS.[1] At this date, 64.7% of patients treated with cabozantinib had disease progression or died (N=121) relative to 67.0% of patients treated with everolimus (N =128).[5] The median PFS for the cabozantinib was 7.4 months (95% CI: 5.6 to 9.1) and 3.8 months (95% CI: 3.7 to 5.4) in the everolimus group.[1] The Kaplain-Meier curves are presented in Figure 4. Cabozantinib was associated with a longer PFS as compared to everolimus (HR: 0.58, 95% CI: 0.45 to 0.75; p-value ≤0.001).[1] Similar estimates were observed at the 31-Dec-2015 analysis (HR: 0.51, 95% CI: 0.41 to 0.62; p-value = ≤0.0001).[2] Sensitivity analyses were also performed to test the robustness of PFS and showed similar estimates.[3,5]

Figure 4: PFS Kaplain-Meier curves using data from the METEOR trial at the 22-May-2015 cut-off date

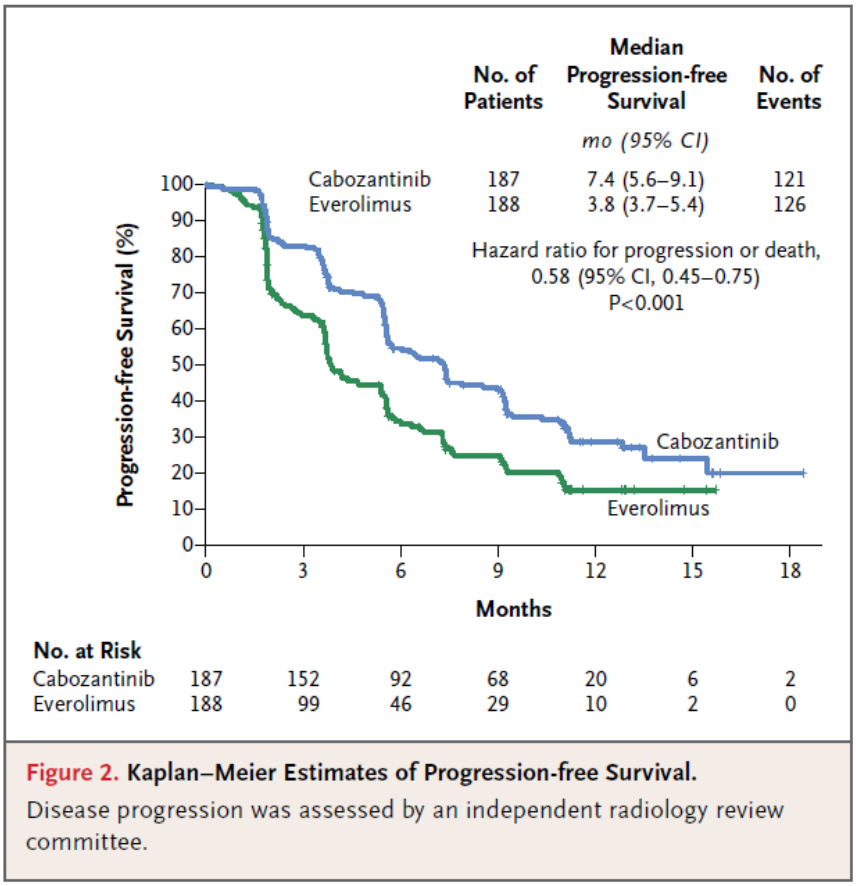
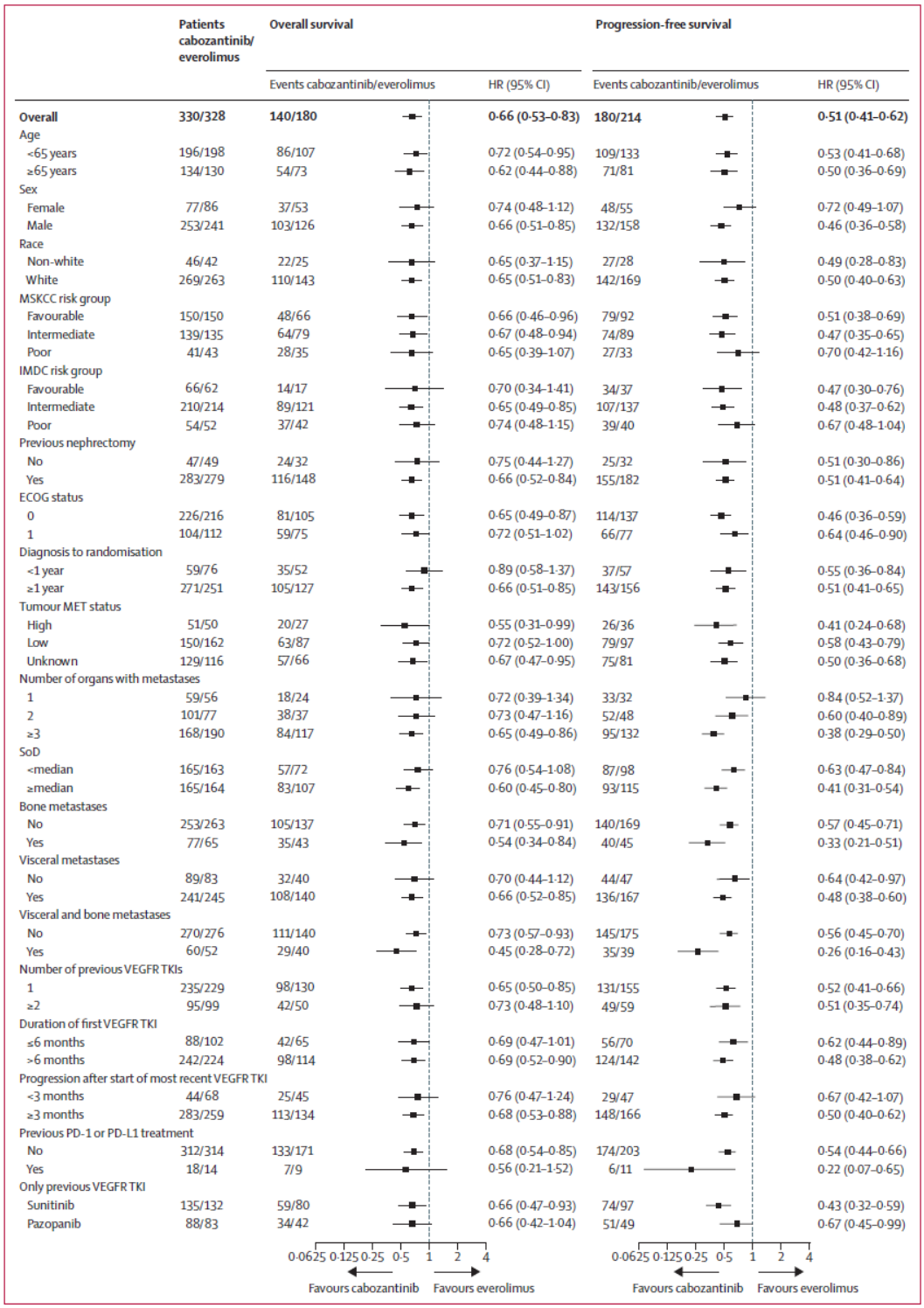


Figure 2. Kaplan–Meier Estimates of Progression-free Survival.
Disease progression was assessed by an independent radiology review committee.

Data Source: Choueiri et al (2015) NEJM[1] From New England Journal of Medicine, Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma Volume 373, No.19, Page No. 1814-23. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Choueiri et al (2016) performed prespecified subgroup analyses testing the effect of cabozantinib versus everolimus on PFS using the 22-May-2015 data cut-off (Figure 5).[2] The estimates from subgroups of interest identified in the protocol were consistent with the overall estimates of PFS.

Figure 5: Subgroup analysis of PFS (22-May-2015) and OS (31-Dec-2015) using data from the METEOR Trial



	Patients cabozantinib/ everolimus	Overall survival		Progression-free survival	
		Events cabozantinib/everolimus	HR (95% CI)	Events cabozantinib/everolimus	HR (95% CI)
Overall	**330/328**	**140/180**	**0·66 (0·53–0·83)**	**180/214**	**0·51 (0·41–0·62)**
Age					
<65 years	196/198	86/107	0·72 (0·54–0·95)	109/133	0·53 (0·41–0·68)
≥65 years	134/130	54/73	0·62 (0·44–0·88)	71/81	0·50 (0·36–0·69)
Sex					
Female	77/86	37/53	0·74 (0·48–1·12)	48/55	0·72 (0·49–1·07)
Male	253/241	103/126	0·66 (0·51–0·85)	132/158	0·46 (0·36–0·58)
Race					
Non-white	46/42	22/25	0·65 (0·37–1·15)	27/28	0·49 (0·28–0·83)
White	269/263	110/143	0·65 (0·51–0·83)	142/169	0·50 (0·40–0·63)
MSKCC risk group					
Favourable	150/150	48/66	0·66 (0·46–0·96)	79/92	0·51 (0·38–0·69)
Intermediate	139/135	64/79	0·67 (0·48–0·94)	74/89	0·47 (0·35–0·65)
Poor	41/43	28/35	0·65 (0·39–1·07)	27/33	0·70 (0·42–1·16)
IMDC risk group					
Favourable	66/62	14/17	0·70 (0·34–1·41)	34/37	0·47 (0·30–0·76)
Intermediate	210/214	89/121	0·65 (0·49–0·85)	107/137	0·48 (0·37–0·62)
Poor	54/52	37/42	0·74 (0·48–1·15)	39/40	0·67 (0·48–1·04)
Previous nephrectomy					
No	47/49	24/32	0·75 (0·44–1·27)	25/32	0·51 (0·30–0·86)
Yes	283/279	116/148	0·66 (0·52–0·84)	155/182	0·51 (0·41–0·64)
ECOG status					
0	226/216	81/105	0·65 (0·49–0·87)	114/137	0·46 (0·36–0·59)
1	104/112	59/75	0·72 (0·51–1·02)	66/77	0·64 (0·46–0·90)
Diagnosis to randomisation					
<1 year	59/76	35/52	0·89 (0·58–1·37)	37/57	0·55 (0·36–0·84)
≥1 year	271/251	105/127	0·66 (0·51–0·85)	143/156	0·51 (0·41–0·65)
Tumour MET status					
High	51/50	20/27	0·55 (0·31–0·99)	26/36	0·41 (0·24–0·68)
Low	150/162	63/87	0·72 (0·52–1·00)	79/97	0·58 (0·43–0·79)
Unknown	129/116	57/66	0·67 (0·47–0·95)	75/81	0·50 (0·36–0·68)
Number of organs with metastases					
1	59/56	18/24	0·72 (0·39–1·34)	33/32	0·84 (0·52–1·37)
2	101/77	38/37	0·73 (0·47–1·16)	52/48	0·60 (0·40–0·89)
≥3	168/190	84/117	0·65 (0·49–0·86)	95/132	0·38 (0·29–0·50)
SoD					
<median	165/163	57/72	0·76 (0·54–1·08)	87/98	0·63 (0·47–0·84)
≥median	165/164	83/107	0·60 (0·45–0·80)	93/115	0·41 (0·31–0·54)
Bone metastases					
No	253/263	105/137	0·71 (0·55–0·91)	140/169	0·57 (0·45–0·71)
Yes	77/65	35/43	0·54 (0·34–0·84)	40/45	0·33 (0·21–0·51)
Visceral metastases					
No	89/83	32/40	0·70 (0·44–1·12)	44/47	0·64 (0·42–0·97)
Yes	241/245	108/140	0·66 (0·52–0·85)	136/167	0·48 (0·38–0·60)
Visceral and bone metastases					
No	270/276	111/140	0·73 (0·57–0·93)	145/175	0·56 (0·45–0·70)
Yes	60/52	29/40	0·45 (0·28–0·72)	35/39	0·26 (0·16–0·43)
Number of previous VEGFR TKIs					
1	235/229	98/130	0·65 (0·50–0·85)	131/155	0·52 (0·41–0·66)
≥2	95/99	42/50	0·73 (0·48–1·10)	49/59	0·51 (0·35–0·74)
Duration of first VEGFR TKI					
≤6 months	88/102	42/65	0·69 (0·47–1·01)	56/70	0·62 (0·44–0·89)
>6 months	242/224	98/114	0·69 (0·52–0·90)	124/142	0·48 (0·38–0·62)
Progression after start of most recent VEGFR TKI					
<3 months	44/68	25/45	0·76 (0·47–1·24)	29/47	0·67 (0·42–1·07)
≥3 months	283/259	113/134	0·68 (0·53–0·88)	148/166	0·50 (0·40–0·62)
Previous PD-1 or PD-L1 treatment					
No	312/314	133/171	0·68 (0·54–0·85)	174/203	0·54 (0·44–0·66)
Yes	18/14	7/9	0·56 (0·21–1·52)	6/11	0·22 (0·07–0·65)
Only previous VEGFR TKI					
Sunitinib	135/132	59/80	0·66 (0·47–0·93)	74/97	0·43 (0·32–0·59)
Pazopanib	88/83	34/42	0·66 (0·42–1·04)	51/49	0·67 (0·45–0·99)

***Figure 3*: Forest plots of overall survival and progression-free survival**
All 658 randomly assigned patients were included in the analyses of overall survival (data cutoff of Dec 31, 2015) and progression-free survival (data cutoff of May 22, 2015). Disease progression and metastatic sites were assessed by an independent radiology review committee. Hazard ratios are estimates from the Cox proportional hazards model and are unstratified with the exception of those for the overall population, which use the stratification factors for randomisation. The available MET data differ between the overall survival and progression-free survival analyses. For the progression-free survival analyses by MET status, the following tumour MET data were available for the cabozantinib group versus the everolimus group: MET high (48 patients *vs* 48 patients), MET low (138 *vs* 151), and unknown MET status (144 *vs* 129). HR=hazard ratio. MSKCC=Memorial Sloan Kettering Cancer Center. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium.[18] ECOG=Eastern Cooperative Oncology Group. SoD=sum of target lesion diameters. TKI=tyrosine-kinase inhibitor.

Data Source: Choueiri et al (2016) Lancet Oncology[2] Reprinted from The Lancet Oncology, Vol. 17 number 7, Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, Page No. 923, Copyright (2016), with permission from Elsevier.

Heng et al (2017) conducted a post-hoc analysis, where they subset the METEOR patient population to include only those who were enrolled in Canada sites (N = 40; $N_{cabozantinib}$ = 23 and $N_{everolimus}$ = 17).[33] Among this subset of Canadian patients, those who were treated with cabozantinib had a median PFS of 7.4 months (95% CI: 4.3 to NE) while those treated with everolimus had a median PFS of 3.7 months (95% CI: 1.7 to 4.7). As previously observed, cabozantinib therapy was associated with a longer PFS as compared to everolimus therapy in patients with RCC (HR: 0.40, 95% CI: 0.17 to 0.89) at the 22-May-2015 data cut-off. However, these results should be interpreted with caution because of small sample sizes. Furthermore, this subgroup analysis was post-hoc, which increases the risk of type 1 error (i.e. false-positives).

Subsequent Therapies and Treatment Continuation

Table 7 represents the subsequent therapies that patients received at the 31-Dec-2015 data cut-off.[2] Half of the patients in the cabozantinib arm and 55% in the everolimus arm received a subsequent therapy. The most common subsequent therapies in the cabozantinib arm were: commercial use everolimus (29%) followed by axitinib (17%). On the other hand, patients were more likely to receive axitinib (27%) in the everolimus arm. Similar estimates were observed at the 02-October-2016 cut-off data.[34]

Among patients who progressed on their current therapy, 38% of patients continued to receive cabozantinib (N=74/193) for more than 2 weeks after radiographic progression while 31% of patients continued to receive everolimus (N=71/226) at the 22-May-2015 data cut-off.[1]

Table 7: Subsequent therapies patients received using the 31-Dec-2015 data cut-off

Table S3: Subsequent Anticancer Therapies

	Cabozantinib N=330 n (%)	Everolimus N=328 n (%)
Systemic therapy	165 (50)	181 (55)
VEGFR-TKI Therapies	79 (24)	155 (47)
Axitinib	57 (17)	90 (27)
Cabozantinib[a]	0	7 (2)
Pazopanib	5 (2)	22 (7)
Sorafenib	9 (3)	31 (9)
Sunitinib	17 (5)	33 (10)
Other Selected Systemic Therapies		
Everolimus[a]	96 (29)	15 (5)
Temsirolimus	6 (2)	4 (1)
Bevacizumab	8 (2)	11 (3)
Interleukins (Interleukin 2)	0	4 (1)
Interferon-α/Peginterferon	5 (2)	7 (2)
PD-1/PD-L1 targeting agents[b]	15 (5)	19 (6)
Chemotherapy	11 (3)	13 (4)
External beam radiotherapy	61 (18)	77 (23)
Surgery (tumour lesions)	13 (4)	9 (3)

Note: patients may have received more than one type of anticancer therapy.
All 658 randomised patients were included in the analysis.
[a] Refers to commercial use.
[b] 14 patients received nivolumab and one received pembrolizumab. In the everolimus arm, 16 patients received nivolumab, two received AMP-514, and one received atezolizumab.
PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

Data Source: Choueiri et al (2016) Lancet Oncology Supplementary Appendix[2]. Reprinted from The Lancet Oncology, Vol. 17 number 7 (Suppl. Appendix), Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, Page No. 6, Copyright (2016), with permission from Elsevier.

Overall Survival

OS was a secondary outcome in the METEOR trial. It was defined as the time from randomization to death due to any cause.[3] Kaplan-Meier analyses to obtain the estimates of OS for each treatment group with corresponding 95% CIs.[3] Differences in treatment effect were tested using a stratified log-rank p-value.[3] Stratified Cox proportional hazard models were also used to estimate the HRs with their corresponding 95% CIs.[3] Formal hypothesis testing was performed for OS.

The 31-Dec-2015 data cut-off was used for the unplanned analysis of OS, which represents a median follow-up of 18.7 months (IQR: 16.1 to 21.1) for patients treated with cabozantinib and 18.8 months (IQR: 16.0 to 21.2) for patients treated with everolimus.[2] Forty-two percent of patients in the cabozantinib group died (N=140) while 55% of patients in the everolimus group died

(N =180).[2] The median OS for the cabozantinib group was 21.4 months (95% CI: 18.7 to NE) and 16.5 months (95% CI: 14.7 to 18.8) in the everolimus group.[2] The Kaplain-Meier curves are presented in Figure 6. Cabozantinib was associated with a longer OS as compared to everolimus (HR: 0.66, 95% CI: 0.53 to 0.83; p-value = 0.00026).[2] Choueiri et al (2016) reported that the OS effect estimate met the criterion for significance based on the alpha spending function (p-value = ≤0.0163).[2] Sensitivity analyses were also performed to test the robustness of OS and showed similar estimates.[3,5]

At the later OS analysis of 2-Oct-2016, 198 patients in the cabozantinib arm and 232 patients in the everolimus arm died.[34] The median OS was 21.4 months (95% CI: 18.7 to NE) in the cabozantinib arm and 17.1 months (95% CI: 14.9 to 18.9) in the everolimus arm. [34] Cabozantinib therapy was associated with a longer OS as compared to everolimus therapy in patients with HCC (HR: 0.70, 95% CI: 0.58 to 0.85; P = 0.0002). [34]

Figure 6: Kaplain-Meier curves of OS using all patients enrolled in the METEOR Trial using the 31-Dec-2015 cut-off

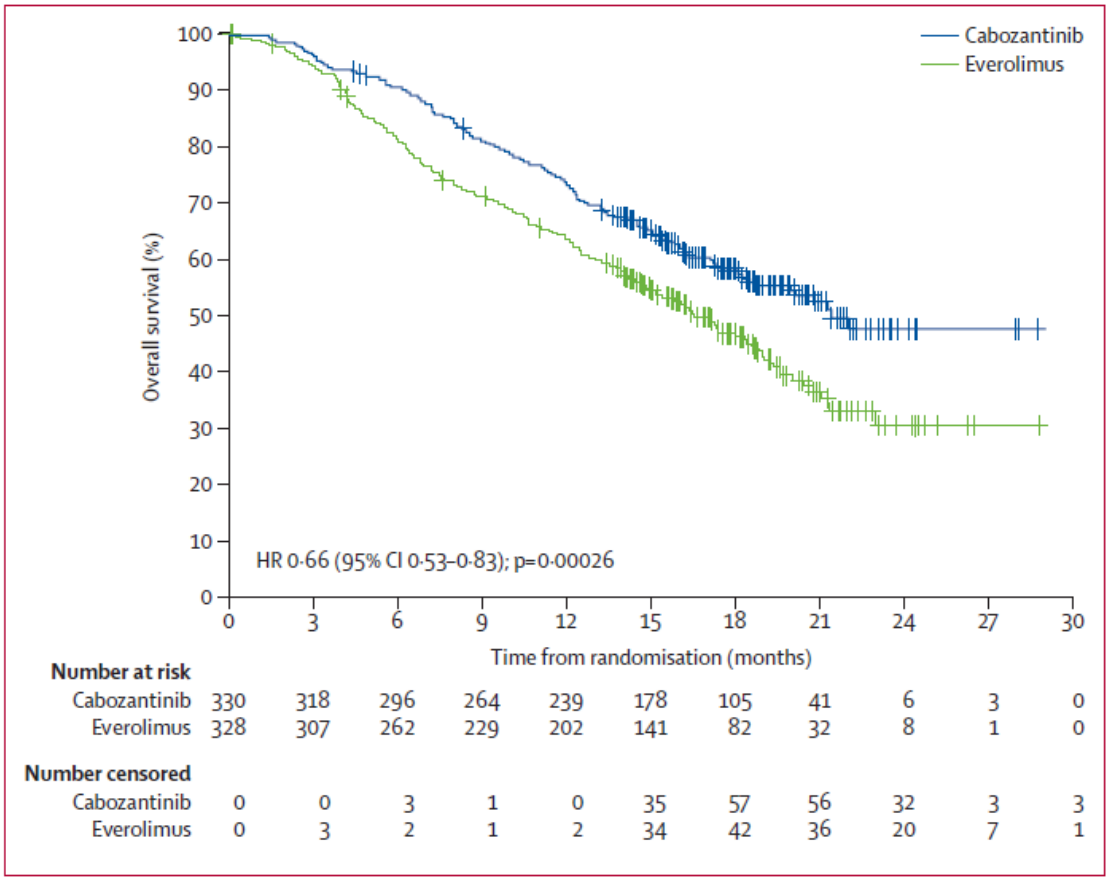


Figure 2: **Kaplan-Meier plot of overall survival through Dec 31, 2015**
All 658 randomly assigned patients were included in the analysis. The number of patients censored is summarised by interval. HR=hazard ratio.

Data Source: Choueiri et al (2016) Lancet Oncology[2] Reprinted from The Lancet Oncology, Vol. 17 number 7, Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, Page No. 922, Copyright (2016), with permission from Elsevier.

Choueiri et al (2016) performed prespecified subgroup analyses testing the effect of cabozantinib versus everolimus on OS in all patients using the 31-Dec-2015 data cut-off (Figure 5).[2] The estimates from subgroups of interest identified in the protocol were consistent with the overall estimates of OS.

In the subset of Canadian patients, those treated with cabozantinib had a median OS of 20.8 months (95% CI: 13.1 to NE) while those treated with everolimus had a median OS of 12.8 months (95% CI: 5.5 to 15.9).[33] Cabozantinib therapy was associated with a longer OS as compared to everolimus therapy in patients with RCC (HR: 0.33, 95% CI: 0.14 to 0.75) at the 31-Dec-2015 data cut-off. However, these results should be interpreted with caution because of small sample sizes, an increased risk of type 1 error and the OS estimates were immature at the time of the analysis.

Objective Response Rate

ORR was another secondary outcome in the METEOR trial and it was defined as the proportion of patients who had measurable disease at baseline and had a complete or partial response as assessed by BIRC using RECIST 1.1, which was confirmed by a subsequent visit ≥ 28 days later.[3] The point estimates of ORR with corresponding 95% CIs and the differences across treatment groups with corresponding 95% CIs were reported.[3] Formal hypothesis testing was performed using the chi-squared test and a two-sided p-value of 0.01.[3]

ORR as assessed by BIRC was reported at the 31-Dec-2015 data cut-off using all randomized patients. There was a significantly higher ORR in the cabozantinib group (ORR: 17%, 95% CI: 13 to 22) as compared to the everolimus group (ORR: 3%, 95% CI: 2 to 6) (p-value ≤ 0.0001).[2] No patients in the trial achieved a complete response. In the Heng et al (2017) post-hoc analysis, the ORR for those treated with cabozantinib was 17% (95% CI 0.14–0.75) and 0% for those treated with everolimus.[33]

Duration of Response and Disease Control Rate

DOR was an exploratory outcomes and it was defined as the time from the last tumor assessment of PR or CR, which was confirmed by a subsequent visit ≥ 28 days later, until the date of documented disease progression as assessed by BIRC.[3] Kaplan-Meier analyses were used to obtain DOR estimates for each treatment group with corresponding 95% CIs.[3] Differences in treatment effect were tested using a stratified log-rank p-value.[3] Stratified Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CIs. There was no adjustment for multiplicity. DCR was not assessed in the study.

EMA reported that the DOR for the cabozantinib arm was NE (95% CI: 7.2 months to NE) and it was 7.4 months (95% CI: 1.9 to NE) in the everolimus arm.[5] In the subgroup by Heng et al (2017), the DOR for those treated with cabozantinib was 9.2 months and 3.7 months for those treated with everolimus.[33]

Quality of Life

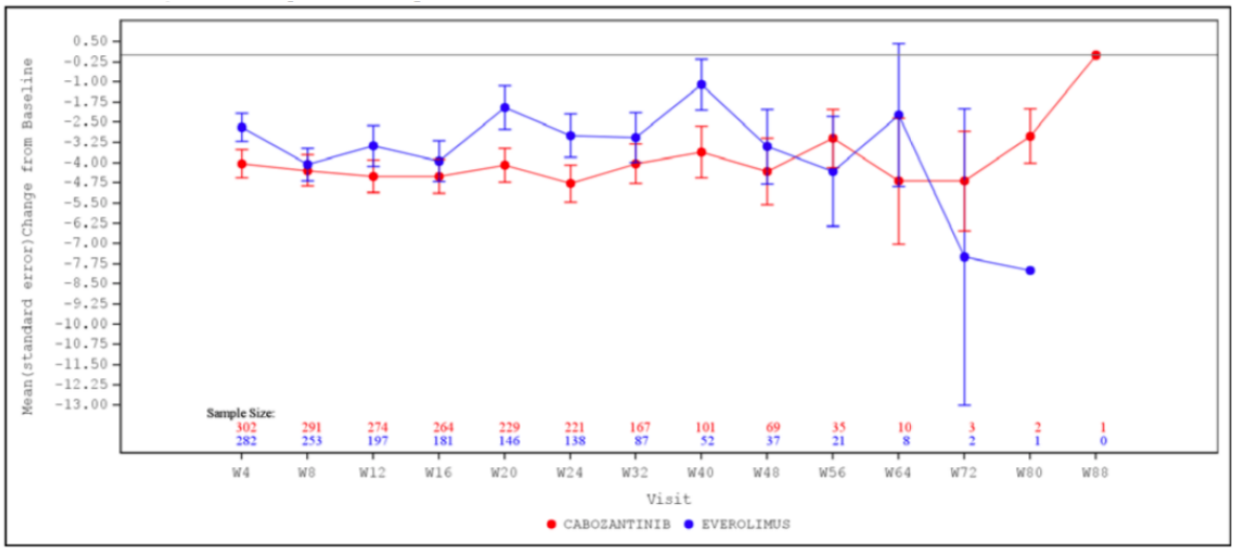
In the METEOR Trial, HRQoL was assessed as a tertiary outcome and it was measured using the FKSI-19 and the EQ-5D-5L questionnaires. The FKSI-19 is a 19-level instrument that assesses the quality of life in patients with renal cancer. Patients can rate their symptoms on a 5-level scale: "not at all, a little bit, somewhat, quite a bit, very much".[3] A better score indicates a better outcome. The MID of the FKSI-19 scale was a ≥ 0.30 change.[6] The EQ-5D-5L provides a standardized measure of health status for five dimensions of health. The EQ-5D-5L also includes an assessment of VAS, which measures patient's health status using a vertical VAS scale that ranges from "Best imaginable health state" to "Worst imaginable health state".[3] The MID of the EQ-5D-5L was a ≥ 0.30 change.[6]

PROs were measured at baseline and then every 4 weeks until week 25 where they were measured every 8 weeks thereafter.[3] Completion rates were derived by dividing the number completed questionnaires by the expected at each time point.[6] For both instruments, a repeated measures mixed-model to compare the change from baseline.[3] The least squares mean (LSM) (and corresponding 95% confidence interval) was used to estimate treatment-specific average change from baseline for each outcome.[6]

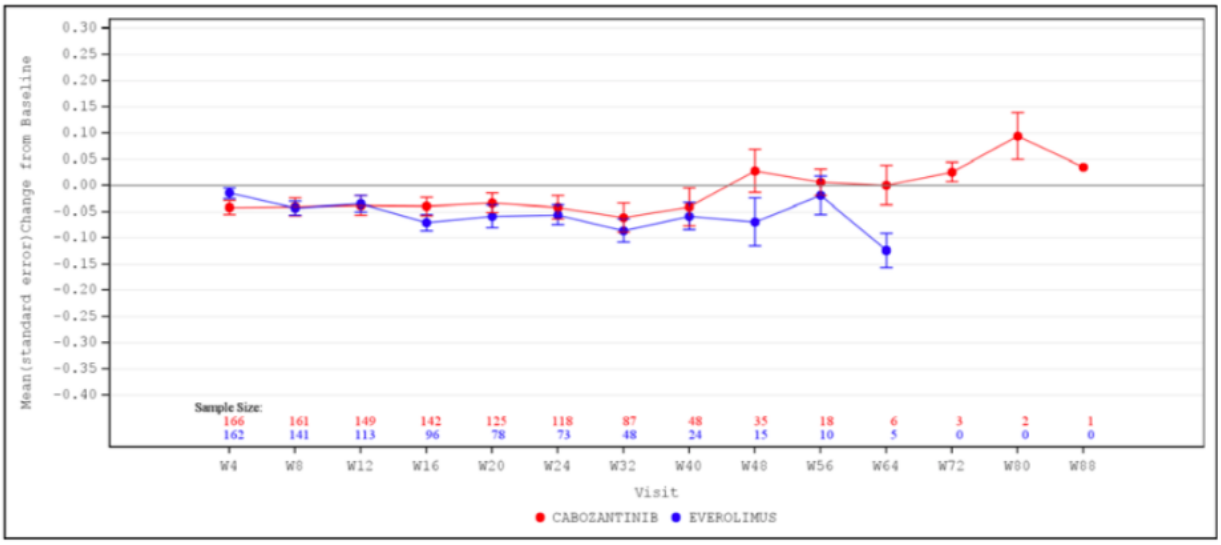
The baseline completion rates were ≥ 95% for both the FKSI-19 the EQ-5D-5L questionnaires (Figure 7).[6] Additionally, for both treatment groups, the completion rate was ≥ 75% for both questionnaires until Week 49.[6] The median duration of completion for the cabozantinib arm was 17 weeks and 13 weeks for the everolimus arm.[6]

Figure 7: The mean change from baseline for (A) the FKSI-19 total score, (B) the EQ-5D-5L score and (C) the EQ-5D-5L VAS score among all patients who were enrolled in the METEOR trial

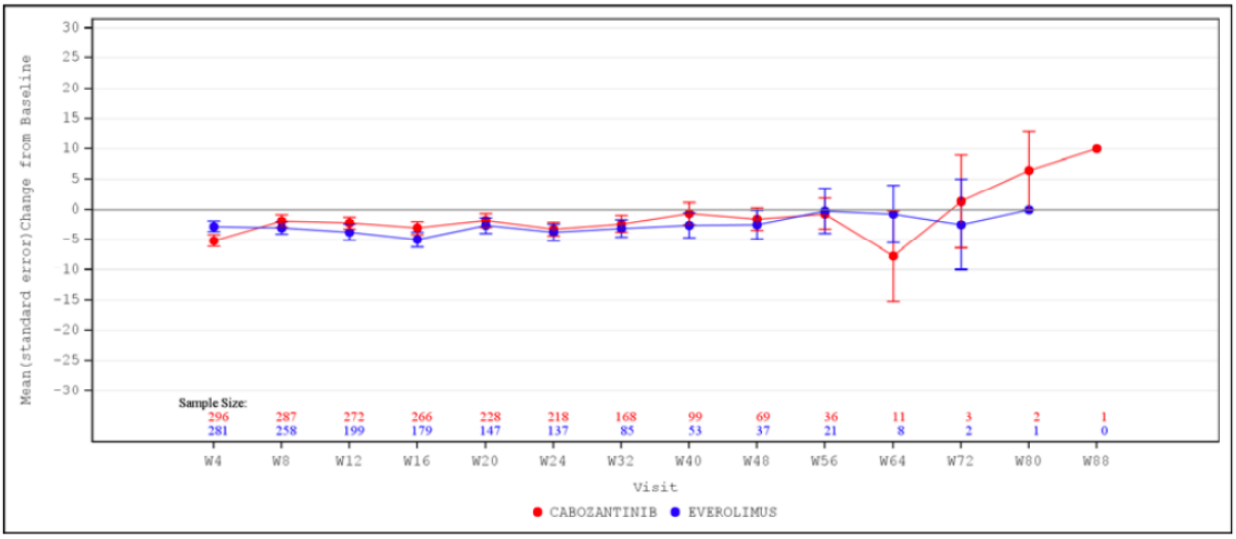
(A) the FKSI-19 total score



(B) the EQ-5D-5L score



(C) the EQ-5D-5L VAS score



Data Source: EMA Report[5] Source: Committee for Medicinal Products for Human Use. Assessment report: Cabometyx. *(European public assessment report)*. London (GB): European Medicines Agency; 2016 Jul 21. https://www.ema.europa.eu/documents/assessment-report/cabometyx-epar-public-assessment-report_en.pdf. Accessed 2019 Jan 03

For the FKSI-19 total score analysis, the difference between treatment arms (i.e. the estimated LSM in change from baseline) was -0.13 (SD_{pooled}: 9.768; p-value <0.0001); a difference that was considered statistically but not clinically significant (MID ≥ 0.30) (Table 8).[6] On the other hand, the difference between treatment arms for the EQ-5D-5L scale (i.e. the estimated LSM in change from baseline) was -0.009 (SD_{pooled}: 0.196; p-value= 0.825) and -0.003 (SD_{pooled}: 16.809; p-value= 0.921) for the EQ-5D-5L VAS scale (Table 8).[6,7] These differences were not considered statistically significant nor clinically significant (MID ≥ 0.30) Overall, it appears that HRQoL was maintained for patients treated with cabozantinib and everolimus and there were no apparent differences between the FKSI-19 and EQ-5D-5L scales over time.

Table 8: Treatment Differences in the FKSI-19, EQ-5D-5L and EQ-5D-5L VAS for all patient in the METEOR Trial

Table 2. Treatment Differences in 19-Item Functional Assessment of Cancer Therapy–Kidney Symptom Index and Four Subscales, Functional Assessment of Cancer Therapy–Kidney Symptom Index-Disease-Related Symptoms, EuroQol-Visual Analog Scale, and EuroQol-Index: Repeated-Measures Change From Baseline Analysis (intent-to-treat population)

Instrument	LS Mean		Difference (95% CI)	Effect Size*
	Cabozantinib	Everolimus		
DRS-Physical	−1.093	−1.386	0.294 (−0.086 to 0.673)	0.046
Lack of energy	−0.244	−0.207	−0.037 (−0.102 to 0.028)	−0.033
Pain	0.125	0.067	0.058 (−0.006 to 0.123)	0.052
Weight loss	−0.533	−0.301	−0.232 (−0.299 to −0.165)	−0.21
Fatigue	−0.325	−0.305	−0.020 (−0.087 to 0.047)	−0.017
Short of breath	0.029	−0.271	0.299 (0.239 to 0.360)	0.30*
Fever	0.056	−0.021	0.077 (0.045 to 0.108)	0.13
Bone pain	0.049	0.057	−0.008 (−0.066 to 0.051)	−0.008
Cough	0.237	−0.059	0.296 (0.238 to 0.354)	0.28
Weak all over	−0.281	−0.265	−0.016 (−0.082 to 0.049)	−0.015
Blood in urine	0.005	−0.001	0.006 (−0.008 to 0.020)	0.023
Good appetite	−0.166	0.181	−0.347 (−0.426 to −0.268)	−0.23
Sleeping well	0.018	−0.152	0.169 (0.095 to 0.243)	0.12
DRS-Emotional	0.398	0.393	0.005 (−0.062 to 0.072)	0.004
Worry condition will get worse	0.398	0.393	0.005 (−0.062 to 0.072)	0.004
Treatment side effects	−2.416	−0.814	−1.602 (−1.744 to −1.459)	−0.62*
Nausea	−0.236	0.069	−0.305 (−0.359 to −0.251)	−0.34*
Diarrhea	−1.280	−0.326	−0.954 (−1.024 to −0.885)	−0.77*
Bothered by side effects of treatment	−0.850	−0.523	−0.327 (−0.401 to −0.253)	−0.24
Function/Well-Being	−0.230	−0.169	−0.061 (-0.247 to 0.124)	−0.019
Able to work	−0.151	−0.101	−0.050 (−0.127 to 0.026)	−0.037
Enjoy life	−0.017	−0.014	−0.003 (−0.073 to 0.066)	−0.002
Content with quality of life right now	−0.035	−0.017	−0.018 (−0.087 to 0.052)	−0.014
FKSI-19 (19-item) Total Score	**−3.483**	**−2.214**	**−1.269 (−1.864 to −0.675)**	**−0.13**
FKSI-DRS (nine-item)	**−0.52**	**−0.93**	**0.409 (0.119 to 0.698)**	**0.087**
EQ-VAS	**−1.32**	**−1.27**	**−0.051 (−1.061 to 0.959)**	**−0.003**
EQ-Index	**−0.02**	**−0.02**	**−0.002 (−0.018 to 0.014)**	**−0.009**

NOTE. A positive mean change (higher score) indicates improved quality of life status.
Abbreviations: DRS, Disease-Related Symptoms; EQ-Index, EuroQol Index; EQ-VAS, EuroQol visual analog scale; FKSI, Functional Assessment of Cancer Therapy–Kidney Cancer Symptom Index; LS Mean, least-squares mean.
*Effect size = treatment difference in mean change from baseline scores/pooled standard deviation for both groups for baseline values. Effect sizes ≥ 0.3 for treatment arm comparisons (denoted with an asterisk) were regarded as likely to be clinically relevant. Positive effect size values favor cabozantinib.

Data source: Cella et al (2018)[6] Reprinted with permission © 2018 American Society of Clinical Oncology. All rights reserved. Cella D, Escudier B, Tannir NM, et al. Quality of Life Outcomes for Cabozantinib Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma: METEOR Phase III Randomized Trial. J Clin Oncol. 2018 Mar 10;36(8):757-764.

Harms Outcomes

A large proportion of patients from the METEOR trial were included in the safety analysis population (99.2%, N = 653).[2] There were 311 patients in the cabozantinib arm and 322 in the everolimus arm.

Dose modification, reductions, delays or discontinuations

At the 31-Dec-2015 cut-off, the median duration of exposure for cabozantinib was 8.3 months (IQR: 4.2 to 14.6) and the median daily dose was 43 mg (IQR: 36 to 56) while the median duration of exposure for everolimus was 4.4 months (IQR: 1.9 to 8.6) and the median daily dose was 9 mg (IQR: 7 to 10 mg).[2] More dose reductions occurred in the cabozantinib group as compared to the everolimus group (62% vs. 25%).[2] The proportion of patients who discontinued treatment due to an AE not related to disease progression was similar between the two groups (cabozantinib: 12% and everolimus: 11%).[2]

The median duration of exposure to cabozantinib was 36 weeks and the median daily dose was 43 mg while the median duration of exposure to everolimus was 19 weeks and the median daily dose was 9.1 mg at the 02-October-2016. [34]

Adverse Events

All Grades and Grade 3 or 4 Adverse Events

Table 9 show a summary of the AEs that occurred in all patients at the 31-Dec-2015 data cut-off.[2] More grade 1-2 AEs occurred in the everolimus arm as compared to the cabozantinib arm (32% vs. 21%) while more grade 3-4 AEs occurred in the cabozantinib group than the everolimus group (71% vs. 60%).[2] At the 31-Dec-2016 cut-off, the most common Grade ≥ 3 AE that occurred in ≥ 10% of patients were anemia (cabozantinib: 6% and everolimus: 17%); hypertension (cabozantinib: 15% and everolimus: 4%); diarrhea (cabozantinib: 13% and everolimus: 2%) and fatigue (cabozantinib: 11% and everolimus: 7%)[2]. Furthermore, the subgroup analysis by Heng et al (2017) demonstrated that the safety profile of the Canadian patients were similar to all patients enrolled in METEOR trial.[33] Likewise, similar estimates were reported at the 02-Oct-2016 data cut-off.[4]

Serious Adverse Events

At the 31-Dec-2015 cut-off, SAEs occurred equally across the two treatment arms (cabozantinib: 39% and everolimus: 40%).[2]

Deaths

One treatment-related death occurred in the cabozantinib group but the cause of death was not specified. In the everolimus arm, two treatment-related deaths occurred due to aspergillus infection and pneumonia aspiration.[2]

Table 9: Summary of the adverse events that occurred in the METEOR safety population

	Cabozantinib (N=331)			Everolimus (N=322)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	70 (21%)	210 (63%)	25 (8%)	103 (32%)	167 (52%)	26 (8%)
Diarrhoea	206 (62%)	43 (13%)	0	85 (26%)	7 (2%)	0
Fatigue	159 (48%)	36 (11%)	0	130 (40%)	24 (7%)	0
Nausea	158 (48%)	15 (5%)	0	92 (29%)	1 (<1%)	0
Decreased appetite	146 (44%)	10 (3%)	0	111 (35%)	3 (1%)	0
Palmar-plantar erythrodysaesthesia syndrome	115 (35%)	27 (8%)	0	16 (5%)	3 (1%)	0
Vomiting	106 (32%)	7 (2%)	0	44 (14%)	3 (1%)	0
Weight decreased	105 (32%)	9 (3%)	0	42 (13%)	0	0
Constipation	89 (27%)	1 (<1%)	0	64 (20%)	1 (<1%)	0
Dysgeusia	80 (24%)	0	0	30 (9%)	0	0
Hypothyroidism	76 (23%)	0	0	1 (<1%)	1 (<1%)	0
Hypertension	73 (22%)	49 (15%)	0	14 (4%)	12 (4%)	0
Dysphonia	68 (21%)	2 (1%)	0	16 (5%)	0	0
Cough	67 (20%)	1 (<1%)	0	107 (33%)	3 (1%)	0
Stomatitis	65 (20%)	8 (2%)	0	71 (22%)	7 (2%)	0
Mucosal inflammation	60 (18%)	5 (2%)	0	64 (20%)	10 (3%)	1 (<1%)
Dyspnoea	56 (17%)	10 (3%)	0	82 (26%)	11 (3%)	3 (1%)
Aspartate aminotransferase increased	55 (17%)	5 (2%)	0	19 (6%)	1 (<1%)	0
Back pain	54 (16%)	8 (2%)	0	41 (13%)	7 (2%)	0
Rash	52 (16%)	2 (1%)	0	92 (29%)	2 (1%)	0
Asthenia	49 (15%)	15 (5%)	0	46 (14%)	8 (2%)	0
Abdominal pain	48 (15%)	12 (4%)	0	27 (8%)	5 (2%)	0
Alanine aminotransferase increased	47 (14%)	7 (2%)	1 (<1%)	20 (6%)	1 (<1%)	0
Pain in extremity	46 (14%)	5 (2%)	0	31 (10%)	1 (<1%)	0
Muscle spasms	45 (14%)	0	0	17 (5%)	0	0
Arthralgia	43 (13%)	1 (<1%)	0	46 (14%)	4 (1%)	0
Headache	43 (13%)	1 (<1%)	0	42 (13%)	1 (<1%)	0
Anaemia	42 (13%)	19 (6%)	0	73 (23%)	53 (17%)	0
Dizziness	41 (12%)	1 (<1%)	0	21 (7%)	0	0
Dyspepsia	40 (12%)	1 (<1%)	0	15 (5%)	0	0
Oedema peripheral	39 (12%)	0	0	70 (22%)	6 (2%)	0
Hypomagnesaemia	38 (12%)	6 (2%)	10 (3%)	5 (2%)	0	0
Dry skin	37 (11%)	0	0	35 (11%)	0	0
Proteinuria	37 (11%)	8 (2%)	0	28 (9%)	2 (1%)	0
Flatulence	33 (10%)	0	0	7 (2%)	0	0
Insomnia	32 (10%)	0	0	33 (10%)	1 (<1%)	0
Pyrexia	31 (9%)	3 (1%)	0	57 (18%)	2 (1%)	0
Pruritus	27 (8%)	0	0	48 (15%)	1 (<1%)	0
Blood creatinine increased	17 (5%)	1 (<1%)	0	39 (12%)	0	0
Hypertriglyceridaemia	17 (5%)	4 (1%)	0	31 (10%)	7 (2%)	3 (1%)
Hyperglycaemia	15 (5%)	2 (1%)	1 (<1%)	46 (14%)	16 (5%)	0
Epistaxis	14 (4%)	0	0	46 (14%)	0	0

Adverse events that were reported as grade 1–2 in at least 10% of the patients in either study group are shown, irrespective of whether the event was considered by the investigator to be related to the study treatment. All grade 3, 4, and 5 events are listed in the appendix (p 10). One treatment-related death occurred in the cabozantinib group (death; not otherwise specified) and two occurred in the everolimus group (one aspergillus infection and one pneumonia aspiration). Patients are counted once at the highest grade for each preferred term. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Table 2: **Adverse events**

Data Source: Choueiri et al (2016) Lancet Oncology[2] Reprinted from The Lancet Oncology, Vol. 17 number 7, Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, Page No. 925, Copyright (2016), with permission from Elsevier.

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of a network meta-analysis comparing the efficacy and safety of anti-cancer therapies in the second line treatment of advanced renal cell carcinoma

Background

The pCODR-conducted literature search identified only one RCT that assessed the efficacy and safety of cabozantinib versus everolimus in patients with advanced RCC who have received prior VEGF TKI.[1,2] Thus, there is a lack of direct evidence comparing cabozantinib to other currently funded therapies in Canada. Given the absence of head-to-head trials, the Manufacturer provided a modified version of the NMA that was published by Amzal et al (2017).[4,29] The NMA was adapted in order to provide an indirect comparison between cabozantinib, everolimus and nivolumab.

Other NMA comparisons have been conducted to compare cabozantinib to other therapeutic agents. The Manufacturer provided an NMA for NICE.[41]

The objective of this section is to summarize and critically appraise the submitted NMA, which provides evidence of the efficacy of cabozantinib as compared to other active therapies in patients with advanced RCC in the second-line setting.

Review of published NMA

Objectives of NMA
The objective of the NMA was to compare the effect of cabozantinib relative to everolimus and nivolumab on the effect of PFS and OS using parametric survival curves.

Methods

Search and Study Selection
The Manufacturer conducted a systematic review to identify eligible studies for the NMA. Studies were eligible for inclusion if included adult patients with advanced, metastatic or previously treated RCC and used a prospective RCT design. The inclusion and exclusion criteria are presented in Table 1.

Table 1: Inclusion and exclusion criteria for systematic review

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously treated advanced or metastatic renal cell carcinoma	Patients <18 years of age
		Healthy subjects
		Animal studies
Intervention	The following interventions in the second- (and further-) line setting: • Cabozantinib (Cabometyx) • Everolimus (Afinitor®) • Nivolumab (Opdivo®) Note: Combination therapies also possible	Interventions in the first-line setting
Comparators	Everolimus or nivolumab	Radiotherapy, surgery and other non-pharmaceutical treatments
Outcomes	• Overall survival • Progression free survival	Patient-reported outcomes Biomarker results

		Safety results
Trial Design	Randomised controlled trial (RCT) Systematic reviews, meta-analyses, HTA for screening of bibliographies only	Non-RCT Comments, letters, editorials Non-systematic reviews
Timeframe	All publication years	
Language restrictions	• English • French • German • Italian • Spanish	Publications with abstract in English but full text in language other than listed in inclusion criteria will not be included but listed.

PubMed, Medline (including Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline) and the Cochrane Library (including: Cochrane Central Register of Controlled Trials, Cochrane Reviews, DARE, HTA Database, NHSEED) were searched to identify relevant articles. The search was performed on 3-Jun-2016. Two reviewers worked independently to screen titles and abstracts, as well as full text articles. If any discrepancies occurred, the investigators used a third party to provide consensus.

The quality of all included studies was reported using an adapted checklist for RCTs from the Centre for Reviews and Dissemination. The adapted checklist assessed randomization method, allocation concealment, homogeneity of baseline characteristics between treatment groups and blinding. The study quality assessment was conducted by two independent reviewers.

NMA Methodology

Prior to conducting the NMA, the authours tested the proportional hazards assumptions of the survival curves from the included studies. It was reported that the proportional hazards assumptions held for the METEOR trial but they were not met for the CheckMate025 trial. Therefore, the authours implemented a Bayesian NMA using parametric curves to explore the effect of cabozantinib to other relevant comparators on efficacy outcomes. This method was selected because it does not assume proportional hazards between the pair-wise comparisons since it compares the shape and scale parameters of each treatment distribution fitted to a survival curve.

The Bayesian NMA used five parametric survival curve functions: log-normal, log-logistic, Weibull, Gompertz and exponential distributions, and these curves were extracted on to PFS and OS curves. This approach was chosen because it facilitates estimation on the pooled data. The rationale for using a fixed effects model over a random effects model was based on the preliminary assessment of heterogeneity and the shorter burn-in time. However, random effects models were reported in additional sensitivity analyses. The model parameters were estimated using a Markov Chain Monte Carlo method on using WinBUGs and a WinBUGs sampler was run for 50,000 iterations with the first 25,000 iterations discarded as “burn-in”. Convergence of the chains was checked using the Gelman-Rubin statistic.

HRs from the NMA were also generated using a fixed effects model even though the proportional hazard assumption was not met.

Results

Included studies

The systematic review performed by the Manufacturer identified a total of 6,612 citations which retrieved 400 full-text articles. Sixty-five articles, referring to 19 studies, were assessed for eligibility. Sixty-four of these articles were initially identified in the search and one paper on the METEOR trial was included even though it was published after the original search. In total, two unique trials, METEOR and CheckMate025, were included in the NMA.

Trial characteristics

Details of the populations, interventions and comparators used in the NMA are reported in Table 2.

Table 2: Assessment of the similarity between identified studies and availability of outcomes and subgroup results

	Study type	Prior therapies	Prognostic score (MSKCC)	Subgroup results available by
METEOR	RCT: Yes Phase: III Double blinded: Open-label Design: parallel	1 prior VEGFR Cabozantinib: 71% Everolimus: 70% 2+ prior VEGFR Cabozantinib: 29% Everolimus: 30%	Favourable: 43-44% Intermediate: 40-43% Poor: 14-16% Missing: 0%	Patient level data available
CheckMate025	RCT: Yes Phase: III Double blinded: Open-label Design: parallel	1 prior VEGFR Nivolumab: 72% Everolimus: 72% 2 prior VEGFR Nivolumab: 28% Everolimus: 28%	Favourable: 35-36% Intermediate: 49% Poor: 15-16% Missing: 0%	Prognostic score: Yes Type of prior therapies: No Number of prior therapies: Yes
Key: RCT, randomised controlled trial; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not applicable; NR, not reported.				

The risk of bias was assessed using an adapted checklist for RCTs as proposed by the Centre for Reviews and Dissemination. It was reported that the risk of bias was low across the included trials. However, there was an increased risk of detection bias for subjective outcomes (i.e., PFS) in the METEOR and CheckMate025 trials because they both used an open-label design. The risk of detection bias was higher in the CheckMate025 trial compared to the METEOR trial. In the CheckMate025 trial, outcome assessors were not blinded to treatment status while a BIRC was used to assess PFS in the METEOR trial.

Prior to conducting the NMA, the authours assessed the assumptions of the NMA. To test transitivity the authours described the study design of the trials and the baseline characteristics as well as assessing the proportional hazards of the PFS and OS Kaplain-Meier curves. The Manufacturer stated that that there were some differences in baseline characteristics across the two trials.

The two trials included in the NMA differed on the number and type of prior therapies. In the METEOR trial, patients had at least one VEGFR TKI while patients had one or two previous regimens of antiangiogenic therapy in the CheckMate025 trial. There appeared to be consistent effect estimates of OS regardless of the number prior therapies in the METEOR and CheckMate025 trials. Similar effect estimates were observed for PFS in the METEOR trial but these estimates

were not reported for PFS in the CheckMate025 trial. The Manufacturer also noted that there is no available information on the type of prior therapies for the CheckMate025.

The MSKCC prognostic score was used to stratify effect estimates for the METEOR and CheckMate025 trials. Due to a lack of data, the Manufacturer were unable to recreate an NMA for MSKCC prognosis. The Manufacturer stated that there was a greater treatment effect on OS for those with a poorer prognosis as compared to those with an intermediate or favourable prognosis in the CheckMate025 trial. In the METEOR trial, there appeared to be a similar treatment effects on OS among those with a poorer, intermediate or favourable prognosis. For PFS, there was a greater treatment effect on PFS for those with an intermediate or favourable prognosis as compared to those with poorer prognosis. PFS estimates were not reported for the CheckMate025 trial.

NMA Results

A graphical representation of the NMA is presented in Figure 1.

Figure 1. Graphical representation of the NMA comparing cabozantinib to nivolumab and everolimus.

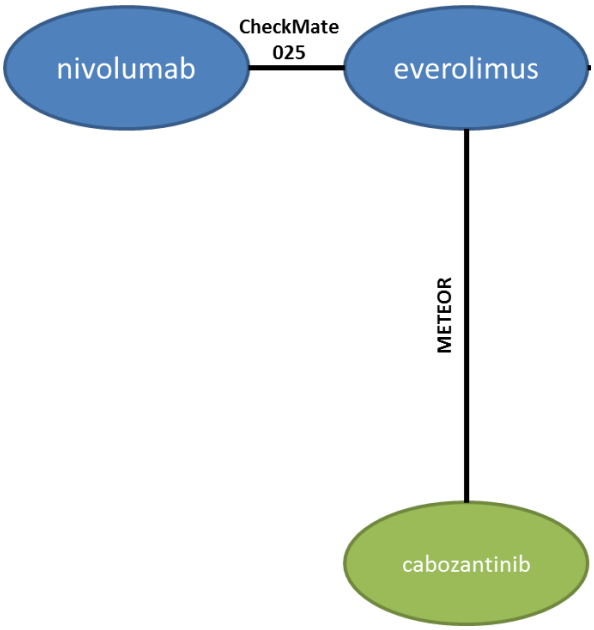


Table 3 shows the direct estimates of PFS and OS for the two trials included in the NMA.

Table 3: Direct estimates of PFS and OS for the METEOR and CheckMate025 trials

HR (95% confidence interval)	OS ITT	PFS Independent review committee (IRC)	PFS Investigator assessed (INV)
METEOR	0.66 (0.53-0.83) Patient level data (published in Figure 2)	0.51 (0.41-0.62) Patient level data (published in Figure 4)	Not applicable
CheckMate025	0.73 (0.57-0.93) Figure 1	Not available	0.88 (0.75-1.03) Figure 2B

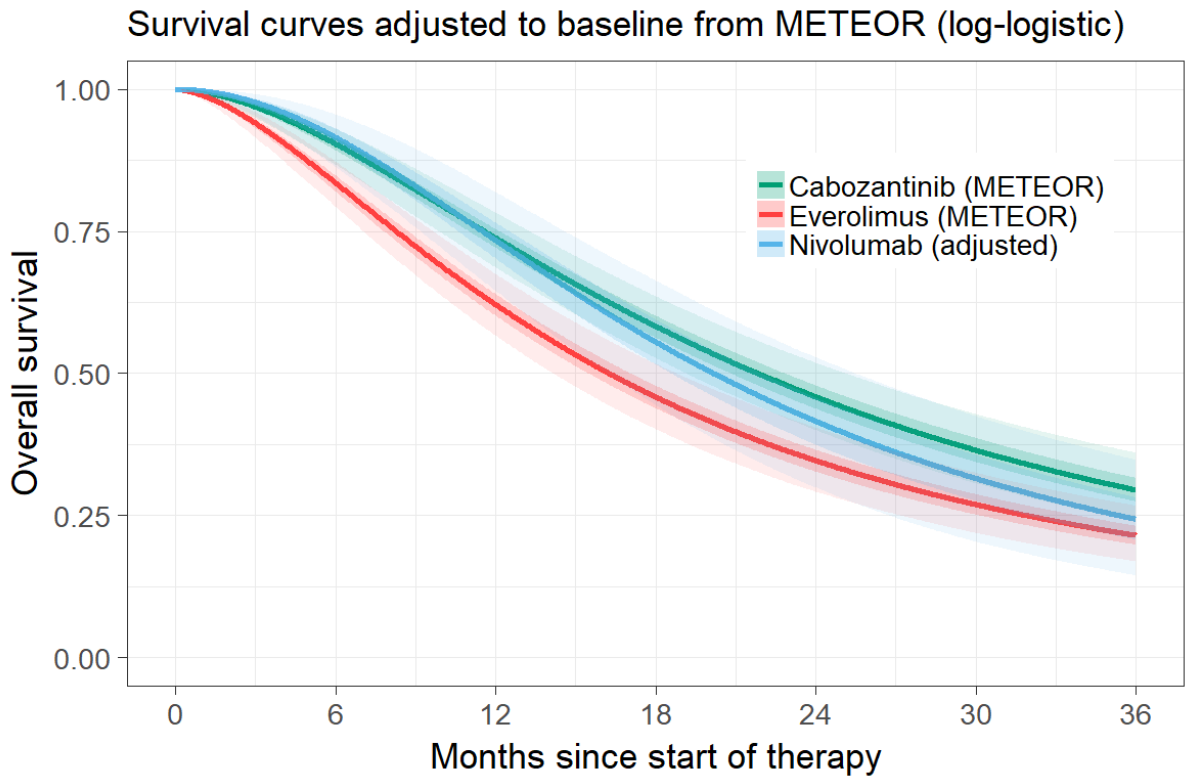
Key: OS, overall survival; ITT, intention to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; INV, investigator assessed; IRC, independent review committee assessed.
Note: ** prior-sunitinib group results used in the analyses.

The Manufacturer conducted a Bayesian NMA based on parametric Kaplain-Meier curves because the proportional hazard assumption was violated. This method is preferred because it does not assume proportional hazards between pairwise comparators. For the NMA of OS and PFS, the Manufacturer implemented five parametric survival curves, which include: log-normal, log-logistic, Weibull, Gompertz and exponential distributions. A fixed-effects approach was used because it provided a better fit as compared to the random-effects model and there was a shorter "burn-in".

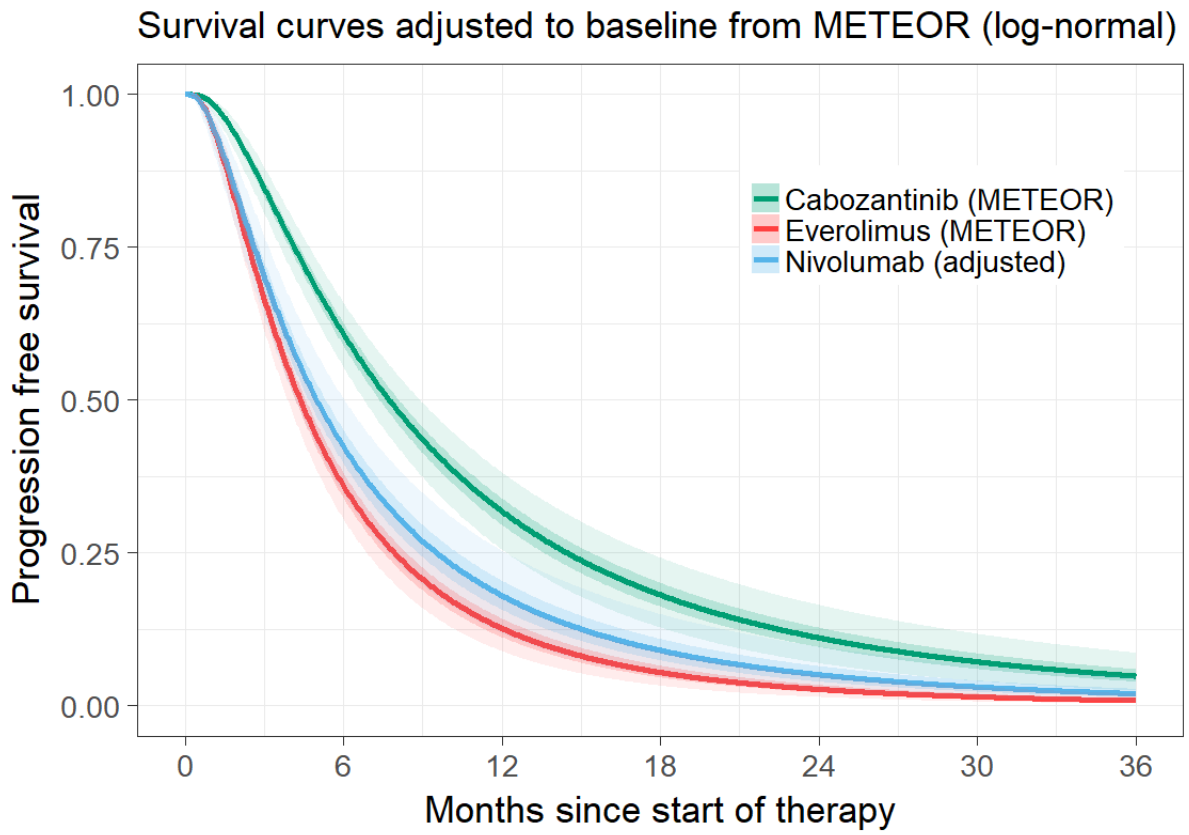
Overall, it was stated that a log-normal model provided the best overall fit for PFS and OS curves as compared to the log-logistic, Weibull, Gompertz and exponential distributions. However, it was then stated that a log-logistic model provided a better fit for OS and a log-normal model provided a better fit for PFS. Both networks were adjusted to the baseline characteristics of the METEOR trial. The Manufacturer observed that cabozantinib was predicted to be superior compared to all other treatments for up to 36 months using a log-logistic distribution for OS and a using a log-normal distribution for PFS. Figure 2 show the average OS and PFS over time using a log-normal fixed effects model.

Figure 2: Average (A) OS and (B) PFS over time derived from a log-logistic and a log-normal fixed-effects model, adjusted to the baseline of the METEOR trial. Shaded areas represent 95% credible intervals.

(A) Overall survival



(B) PFS



Although the proportional hazards assumption was not met for the Checkmate025 trial, the Manufacturer compared the HRs of the three treatment groups using an NMA. Table 4 represents the results of the OS and the PFS NMA using a fixed effects model. If available, PFS as assessed by IRC estimates were used in the model. These results should be interpreted with caution because the proportional hazards assumption was not met for all of the treatment comparators and it cannot be assumed that the HR remains constant over time.

Table 4: Network meta-analysis of OS and PFS (IRC-assessed when available) hazard ratios

A) OS

	HR (95% credible intervals)		
	Cabozantinib	**Everolimus**	**Nivolumab**
Cabozantinib	NA	0.66 (0.53, 0.83)	0.9 (0.69, 1.19)
Everolimus	1.52 (1.21, 1.9)	NA	1.37 (1.17, 1.61)
Nivolumab	1.11 (0.84, 1.46)	0.73 (0.62, 0.86)	NA

B) PFS

	HR (95% credible intervals)		
	Cabozantinib	**Everolimus**	**Nivolumab**
Cabozantinib	NA	0.51 (0.42, 0.62)	0.58 (0.45, 0.74)
Everolimus	1.96 (1.62, 2.37)	NA	1.14 (0.97, 1.33)
Nivolumab	1.73 (1.35, 2.21)	0.88 (0.75, 1.03)	NA

Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[43] Details of the critical appraisal are presented below.

Table 5: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al[43]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes.** The study populations of all the included trials in the NMA matched in review indication, which was to evaluate the efficacy and safety of cabozantinib in patients with advanced RCC who have received VEGF TKI therapy.
2. Are any critical interventions missing?	**No.** The Manufacturer included all relative interventions for this patient population in the systematic review.
3. Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were assessed: OS and PFS. Other relative outcomes for this patient population were excluded from the systematic review and NMA: patient-reported outcomes and safety results.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the three included trials were similar.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** A summary of the systematic literature review process used in the NMA was reported. The information sources, search strategy and study selection criteria were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the NMA.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Manufacturer used an adapted checklist for RCTs proposed by the Centre for Reviews and Dissemination to assess the quality of the included trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
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?	**Yes.** The Manufacturer provided a qualitative assessment of the treatment modifiers.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different	**Yes.** The Manufacturer noted an imbalance in effect modifiers across the different treatment comparisons identified prior to comparing individual study results. There were differences in type and number of previous therapies and baseline prognostic factors.

ISPOR Questions	Details and Comments‡
treatment comparisons identified prior to comparing individual study results?	
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes.**
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?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
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?	**Yes, in part.** It was concluded that a Bayesian NMA using parametric curves was a more suitable.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The Manufacturer stated that fixed effect models were used due to the lack of heterogeneity and the burn-in time was shorter.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Unclear.** Subgroup analyses or meta-regression analyses were not performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the NMA and the violation of the proportional hazard assumption.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The NMA is presented in Figure 1.
19. Are the individual study results reported?	**Yes.** The Manufacturer provided the baseline characteristics of the trials and the effect estimates of all outcomes used in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Manufacturer has provided the direct comparisons of PFS and OS for all of the trials included in the NMA.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes, in part.** An NMA method based on parametric survival models was chosen and implemented. Despite the violation of the proportional hazard assumption, an NMA using HR estimates was performed.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	**Yes, in part.** The overall conclusions of the NMA are limited because there were considerable differences in the study design and baseline population characteristics of the included studies. Therefore, the NMA should be interpreted with caution.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not reported.**

Conclusion

The Manufacturer submitted an NMA that compared cabozantinib to nivolumab and everolimus in patients with advanced RCC who progressed after treatment with VEGF TKIs. The Manufacturer made indirect comparisons using parametric survival curves because the proportional hazards assumption was violated for some trials. The results of the NMA indicate that patients on cabozantinib had a greater likelihood of PFS and OS as compared to those treated with the other comparators. The overall conclusions of the NMA are limited because there were considerable differences in the study design and baseline population characteristics of the included studies. Therefore, the NMA should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Renal 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 cabozantinib (Cabometyx) for renal cell carcinoma (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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2018, **Embase** 1974 to 2018 September 21, **Ovid MEDLINE(R) ALL** 1946 to September 21, 2018

Search Strategy:

#	Searches	Results
1	(Cabometyx* or Cabozantinib* or BMS-907351 or BMS907351 or XL-184 or XL184 or 849217-68-1 or 1140909-48-3).ti,ab,ot,kf,kw,hw,rn,nm.	3417
2	Kidney Neoplasms/ or Carcinoma, Renal Cell/ or (((renal or collecting duct? or hypernephroid or hyper-nephroid or kidney* or nephroid) adj3 (adenocarcinoma? or adeno-carcinoma? or carcinoma? or cancer* or neoplasm* or tumor* or tumour*)) or hypernephrom* or hyper-nephrom* or (grawitz adj (tumor* or tumour*))).ti,ab,kf,kw.	185629
3	1 and 2	679
4	3 use cctr	71
5	3 use medall	152
6	4 or 5	223
7	*Cabozantinib/ or (Cabometyx* or Cabozantinib* or BMS-907351 or BMS907351 or XL-184 or XL184).ti,ab,kw.	1820
8	Kidney Carcinoma/ or Renal Cell Carcinoma/ or (((renal or collecting duct? or hypernephroid or hyper-nephroid or kidney* or nephroid) adj3 (adenocarcinoma? or adeno-carcinoma? or carcinoma? or cancer* or neoplasm* or tumor* or tumour*)) or hypernephrom* or hyper-nephrom* or (grawitz adj (tumor* or tumour*))).ti,ab,kw.	172844
9	7 and 8	503
10	9 use oemezd	288

11	conference abstract.pt.	3191697
12	10 and 11	96
13	limit 12 to yr="2013 -Current"	90
14	10 not 11	192
15	13 or 14	282
16	6 or 15	505
17	limit 16 to english language	474
18	remove duplicates from 17	307

2. Literature search via PubMed

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

Search	Query	Items found
#6	Search **#3 AND #4** Filters: **English**	11
#5	Search **#3 AND #4**	11
#4	Search **publisher[sb]**	535322
#3	Search **#1 AND #2**	164
#2	Search **Cabozantinib[Supplementary Concept] OR cabozantinib*[tiab] OR Cabometyx*[tiab] OR BMS-907351[tiab] OR BMS907351[tiab] OR XL-184[tiab] OR XL184[tiab] OR 849217-68-1[tiab] OR 1140909-48-3[tiab]**	611
#1	Search **((renal[tiab] OR collecting duct*[tiab] OR hypernephroid[tiab] OR hyper-nephroid[tiab] OR kidney*[tiab] OR nephroid[tiab]) AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR tumOR*[tiab] OR tumour*[tiab])) OR hypernephrom*[tiab] OR hyper-nephrom*[tiab] OR (grawitz[tiab] AND (tumor*[tiab] OR tumour*[tiab]))**	121199

3. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

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

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

Search: Cabometyx/cabozantinib, renal cell carcinoma (RCC)

Select international agencies including:

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

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

Search: Cabometyx/cabozantinib, renal cell carcinoma (RCC)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources

Search: Cabometyx/cabozantinib, renal cell carcinoma (RCC) – last 5 years

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) 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 imfinzi/durvalumab) and nonsmall cell lung cancer (NSCLC).

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

The search is considered up to date as of January 2, 2019.

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

Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

REFERENCES

1. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1814-1823.
2. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(7):917-927.
3. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. METEOR trial protocol. *N Engl J Med*. 2015;373(19):Supplementary material. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1510016/suppl_file/nejmoa1510016_protocol.pdf. Accessed 2019 Jan 7.
4. pan-Canadian Oncology Drug Review manufacturer submission: cabometyx (cabozantinib), 20mg, 40mg, 60mg tablets. Ipsen Biopharmaceuticals Canada Inc. Mississauga (ON): Ipsen Biopharmaceuticals Canada Inc.; 2018 Sep 17.
5. Committee for Medicinal Products for Human Use. Assessment report: Cabometyx (cabozantinib). London (GB): European Medicines Agency; 2016 Jul 21: https://www.ema.europa.eu/documents/assessment-report/cabometyx-epar-public-assessment-report_en.pdf. Accessed 2019 Jan 7.
6. Cella D, Escudier B, Tannir NM, et al. Quality of Life Outcomes for Cabozantinib Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma: METEOR Phase III Randomized Trial. *J Clin Oncol*. 2018;36(8):757-764.
7. IPSEN Biopharmaceuticals Canada checkpoint meeting questions on cabozantinib (Cabometyx) for advanced renal cell carcinoma [additional manufacturer's information]. Mississauga (ON): IPSEN Biopharmaceuticals Canada; 2018 Nov 6.
8. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. Special topic: pancreatic cancer. Toronto (ON): Canadian Cancer Society; 2017: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2017-EN.pdf?la=en. Accessed 2019 Jan 8.
9. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer*. 2008;113(1):78-83.
10. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med*. 1998;338(18):1272-1278.
11. Negrier S, Perol D, Ravaud A, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer*. 2007;110(11):2468-2477.
12. Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *N Engl J Med*. 1998;338(18):1265-1271.
13. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002;20(1):289-296.
14. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23(4):832-841.
15. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27(34):5794-5799.
16. Rini BI. VEGF-targeted therapy in metastatic renal cell carcinoma. *Oncologist*. 2005;10(3):191-197.
17. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med*. 2016;375(23):2246-2254.
18. Jewett MA, Knox JJ, Kollmansberger C, Basiuk J. Canadian kidney cancer forum 2008. *Can Urol Assoc J*. 2008;2(3):183.

19. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115-124.
20. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722-731.
21. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356(22):2271-2281.
22. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.
23. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.
24. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer*. 2010;116(18):4256-4265.
25. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14(6):552-562.
26. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.
27. Motzer RJ, Sharma P, McDonald E, et al. CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC). 2016 Jan 6; https://meetinglibrary.asco.org/record/120071/abstract. Accessed 2019 Jan 8.
28. Albiges L, Fay AP, Xie W, et al. Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma. *Eur J Cancer*. 2015;51(17):2580-2586.
29. Amzal B, Fu S, Meng J, Lister J, Karcher H. Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma. *PLoS One*. 2017;12(9):e0184423, 0182017.
30. Donskov F, Motzer RJ, Voog E, et al. Outcomes based on age in the phase 3 METEOR trial of cabozantinib (cabo) vs everolimus (eve) in patients with advanced renal cell carcinoma (RCC). *J Clin Oncol*. 2017;35(15 Supplement 1).
31. Grande E, Choueiri TK, Motzer RJ, et al. Effect of prior systemic therapy on clinical outcomes with cabozantinib vs everolimus in advanced renal cell carcinoma: Results from the phase 3 METEOR study. *Eur J Cancer*. 2017;72 (Supplement 1):S197-S198.
32. Escudier B, Powles T, Motzer RJ, et al. Cabozantinib, a New Standard of Care for Patients With Advanced Renal Cell Carcinoma and Bone Metastases? Subgroup Analysis of the METEOR Trial. *J Clin Oncol*. 2018;36(8):765-772.
33. Heng D, Kollmannsberger C, Basappa N, et al. Clinical outcomes for Canadian patients in the phase 3 METEOR study of cabozantinib vs. everolimus in advanced renal cell carcinoma. *Can Urol Assoc J*. 2017;6(Supplement 4):S258.
34. Motzer RJ, Escudier B, Powles T, Scheffold C, Choueiri TK. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. *Br J Cancer*. 2018;118(9):1176-1178.
35. Pal SK, Motzer RJ, Fishman MN, et al. Analysis of overall survival (OS) based on tumor target lesion change in the phase 3 METEOR trial of cabozantinib (cabo) versus everolimus (eve) in advanced renal cell carcinoma (RCC). *J Clin Oncol*. 2017;6(Supplement 1).
36. Powles T, Motzer RJ, George DJ, et al. Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib (c) vs everolimus (e) in advanced renal cell carcinoma (rcc). *Ann Oncol*. 2017;28 (Supplement 5):v307-v308.
37. Powles T, Motzer RJ, Escudier B, et al. Outcomes based on prior therapy in the phase 3 METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma. *Br J Cancer*. 2018;10:10.

38. Schmidinger M, Motzer RJ, Powles T, et al. Overall survival results from the phase 3 trial of cabozantinib vs everolimus in advanced renal cell carcinoma (METEOR). *Eur J Cancer*. 2017;72 (Supplement 1):S187-S188.
39. Tannir N, Powles T, Motzer RJ, et al. Analysis of regional differences in the phase 3 METEOR study of cabozantinib (cabo) versus everolimus (eve) in advanced renal cell carcinoma (RCC). *Ann Oncol*. 2016;27(Supplement 6):818P.
40. Exelixis. NCT01865747: A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR). *ClinicalTrials.gov*. Bethesda (MD): National Library of Medicine; 2013: https://clinicaltrials.gov/ct2/show/NCT01865747. Accessed 2019 Jan 7.
41. National Institute for Health Care and Excellence. Cabozantinib for previously treated advanced renal cell carcinoma. *Single technology appraisal ID931* 2017; https://www.nice.org.uk/guidance/ta463/documents/committee-papers. Accessed 2019 Jan 7.
42. Hessel C, Mangeshkar M, Motzer RJ, et al. Evaluation of the novel "trial within a trial" design of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC). *Ann Oncol*. 2016;27(Supplement 6).
43. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17(2):157-173.