Canada's Drug Agency
L'Agence des médicaments du Canada

Cabozantinib for epNETs or pNETs

FMEC Responses to Questions from the Drug Programs

Table 1: Response Summary

Drug Program Implementation Questions	Clinical Expert Response (Clinical Experts Acting as Guest Specialists for FMEC)	FMEC Response
Considerations for Relevant Comparators		
The CABINET trial compared cabozantinib to placebo in patients with advanced NETs who had progressed after at least one prior therapy, including everolimus and other drugs. However, in clinical practice, most patients receive active treatments. Is it reasonable to use a placebo as a comparator in this trial?	The clinical experts highlighted that while all patients had to have at least one prior therapy, the availability of other treatments in some instances complicates the situation. For some patients, a placebo would be an appropriate comparator, especially if they had already exhausted multiple lines of therapy and had no other treatment options available. However, in some instances there are other therapies available that would make a placebo-controlled trial problematic. In clinical practice, most patients typically receive active treatments. Nonetheless, for those who had exhausted all previous therapies, a placebo would be a reasonable choice.	FMEC agrees with the clinical experts.
Policy Considerations		
In the CABINET trial, researchers determined patient disease progression (measurable disease) using RECIST 1.1 criteria. Should we use the same criteria to assess disease progression in clinical practice in Canada?	The clinical experts have noted that physicians employ RECIST 1.1 to assess disease progression.	FMEC notes that clinicians should not have to follow the RECIST criteria which are for clinical trials to evaluate response to cabozantinib. These criteria are also difficult to implement in clinical practice setting. Clinicians should follow their usual practices to determine disease progression.
The CABINET trial excluded the following patients: • Patients with class III/IV congestive heart failure or a history of long QT syndrome • Patients with lung lesions (cavitary and endobronchial lesions) • Patients with brain metastases or cranial epidural disease Would any of these patients be eligible to receive cabozantinib therapy?	Both clinical experts agree that the risk-benefit ratio of treatment should be assessed and discussed with the patient. Because cabozantinib is a VEGFR2 inhibitor and carries a risk of bleeding, patients with a high bleeding risk should be excluded from treatment.	FMEC defers to the clinical experts.
In the CABINET trial, patients who received at least one prior therapy either experienced disease progression or intolerance were eligible to receive cabozantinib. Importantly, not all patients had been treated with everolimus.	One clinical expert emphasized that everolimus carries significant toxicity and may not be suitable for all patients. In pNETs, more tolerable first-line treatment options are available, and cabozantinib should be	FMEC defers to the clinical experts related to the place in therapy for cabozantinib but wishes to clarify that SSAs are not included as the prior

Are all patients who have received at least one prior therapy, regardless of type, eligible to receive cabozantinib?	considered for patients who have received at least one prior therapy, regardless of the specific agent. This expert also explained that, in clinical practice, treatment for epPNETs typically follows a sequence of SSRA, then PRRT, followed by cabozantinib. For pNETs, several systemic therapies may be used before cabozantinib. In lung NETs, everolimus may be used prior to cabozantinib, though SSRAs are commonly the first-line treatment, with PRRT used in some cases—acknowledging that access to PRRT varies across jurisdictions. Another clinical expert noted that whether everolimus is superior to cabozantinib remains unknown, because they have not been evaluated in head-to-head comparative trials. It is generally established that cabozantinib is superior to placebo after at least one line of approved therapy (not including SSA). While other active treatments may be appropriate for some patients, their effectiveness compared to cabozantinib has not been fully established.	line of therapy for eligibility for cabozantinab.
Can cabozantinib be administered to patients who have been off-treatment or have relapsed?	Both clinical experts agree that cabozantinib can be administered to these patients.	FMEC defers to the clinical experts.
Discontinuation of therapy		
Disease progression was measured based on RECIST 1.1 criteria in the CABINET study. Could you provide the criteria for discontinuing cabozantinib in clinical practice?	The clinical experts indicated that evidence of progression as per RECIST 1.1 or intolerance to therapy is appropriate discontinuation criteria.	FMEC notes that the RECIST criteria is not applicable in clinical practice.
If there is disease progression during a "drug holiday (i.e., treatment interruptions)", can cabozantinib treatment be resumed? What is the recommended timeframe for resuming treatment?	Both clinical experts stated that the recommended timeframe is at least three months. Treatment interruptions are entirely acceptable given that these patients may be on therapy for an extended period.	FMEC defers to the clinical experts.
Prescribing of Therapy		
Cabozantinib is available in 60 mg, 40 mg, and 20 mg tablets. Is the recommended daily dose of 60 mg suitable for various jurisdictions and consistent with other indications?	Both clinical experts agree that the median dose in the trial was slightly below 40 mg, with the majority of patients requiring dose reductions. In clinical practice, most patients are expected to start at 40 mg, with dose escalation as tolerated.	FMEC defers to the clinical experts.
Special Implementation Issues (Generalizability)		
The CABINET trial required patients with an ECOG score of 0-2 for eligibility, but the majority of patients reported with a ECOG score of 0 or 1.	Both clinical experts agree that ECOG 2 patients should be eligible to receive cabozantinib.	FMEC agrees with the clinical experts.

Can patients with an ECOG score of 2 or greater receive or be eligible for cabozantinib for advanced NETs?		
How does using a placebo comparator in the CABINET trial impact the generalization of evidence to clinical practice in Canada?	Both clinical experts indicated that there would be no impact on the generalizability; the CABINET is generalizable to the broader population of NETs patients in Canada.	FMEC defers to the clinical experts.

ECOG= Eastern Cooperative Oncology Group; NET = neuroendocrine tumours; pNETs = pancreatic neuroendocrine tumours; PRRT = Peptide Receptor Radionuclide Therapy; RECIST = Response Evaluation Criteria in Solid Tumors; SSA = Somatostatin Analogs; SSRA = Somatostatin Receptor Analogs; VEGF2 = Vascular Endothelial Growth Factor Receptor 2