Reimbursement Review

Cabozantinib(N/A)

Draft Review Report

Requester: Public drug programs

Therapeutic area: Neuroendocrine tumours

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Key Messages

What are locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours?

- Neuroendocrine tumours (NETs), including extra-pancreatic (epNETs) and pancreatic (pNETs) types, originate from secretory cells and can occur in various organs. These tumors can be functional, causing various symptoms, or nonfunctional. These tumors significantly impact individuals' quality of life and functional performance.
- In Canada, an Ontario-based study (2015) reported an increase in incidence from 2.46 per 100,000 to 5.86 per 100,000 over 15 years, with pNETs accounting for about 10% of cases.

What are the Treatment Goals and Current Treatment Options for locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours?

- The treatment goals for patients with locally advanced or metastatic neuroendocrine tumors are to prolong life, delay disease progression, reduce cancer-related symptoms, prevent treatment complications, and improve or maintain patients' functioning and quality of life.
- Treatment approaches vary based on various factors, such as tumour grade, differentiation, functionality, and other factors for both epNETs and pNETs. The treatment options include:
    - For localized solid tumors: surgical resection is the first-line treatment
    - For unresectable tumors, systemic therapy options include:
        - Somatostatin analogues: Initial therapy for unresectable metastatic disease or hormonal overproduction syndromes.
        - Targeted agents: Options include everolimus, sunitinib, and cabozantinib for patients who have progressed on somatostatin analogues.
        - Chemotherapy agents: for example, capecitabine plus temozolomide
        - Peptide Receptor Radionuclide Therapy: generally considered after somatostatin analogues

What is cabozantinib?

- Cabozantinib is a tyrosine kinase inhibitor that is available as an oral tablet. Health Canada has approved cabozantinib for renal cell carcinoma, hepatocellular carcinoma, differentiated thyroid carcinoma, but there is not an indication for neuroendocrine tumours.

Why Did We Conduct This Review?

- At the request of the participating public drug programs, we reviewed cabozantinib to inform a recommendation on whether it should be reimbursed for adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy.

How Did We Evaluate cabozantinib?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of cabozantinib versus other treatments in Canada or placebo in adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy.
- The clinical evidence was identified through systematic searches for available studies.

- The review was also informed by 1 clinician group submissions and 1 patient group submission in response to our call for input, and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation. We consulted 2 clinical experts in neuroendocrine tumours as part of the review process.

What Did We Find?

Clinical Evidence

- We reviewed a phase 3, multicentre, double-blinded, randomized trial (the CABINET trial) comparing the efficacy and safety of cabozantinib with placebo in adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy.
- Cabozantinib improved progression-free survival compared to placebo. Uncertainties arose from the early termination of the study (which might overestimate cabozantinib's effect), small sample size, and limited information to appraise the potential for missing data. Clinical experts consulted by the review team indicated that the benefit was clinically meaningful.
- The evidence was insufficient to demonstrate a benefit on overall survival for cabozantinib compared to placebo; there were wide CIs that crossed the null, with the point estimate near the null for the pNET cohort. This may be influenced by the trial being underpowered for overall survival and the allowance of crossover from the placebo group to the cabozantinib group.
- The trial only reported descriptive results with a high risk of bias regarding health-related quality of life, which is important to patients. Results of formal analyses of quality of life were not available. Based on the descriptive data on health-related quality of life, the overall health-related quality of life remained stable over time and was similar in both the cabozantinib and placebo groups among patients who completed questionnaires in the epNET and pNET cohorts.
- Compared to the placebo group, patients in the cabozantinib group reported higher proportions of adverse events, serious adverse events, and discontinuation due to adverse events.[1]
- Evidence on the benefits and harms of cabozantinib as compared with other relevant comparators is unavailable.

Economic Evidence

- Reimbursing cabozantinib for adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
CAPTEM	chemotherapy such as capecitabine plus temozolomide
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
epNET	extra-pancreatic neuroendocrine tumors
FDA	Food and Drug Administration
HRQoL	health-related quality of life
ITT	intention to treat
NET	neuroendocrine tumors
OS	overall survival
PFS	progression-free survival
pNET	pancreatic neuroendocrine tumors
PRRT	peptide receptor radionuclide therapy
QoL	quality of life
RCT	randomized controlled trial
SSAs	somatostatin analogues
HR	hazard ratio
AE	adverse event
SAE	serious adverse event
WDAE	withdrawal due to adverse event
WHO	World Health Organization

Background

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of cabozantinib in the treatment of adults with locally advanced or metastatic extra-pancreatic (epNET) or pancreatic neuroendocrine tumours (pNET) who have received at least 1 prior therapy. The focus will be placed on comparing cabozantinib to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for cabozantinib compared with relevant comparators for the same population. The comparators considered relevant to the reviews were somatostatin analogs: lanreotide or octreotide, everolimus, sunitinib, streptozocin plus doxorubicin plus 5-fluorouracil, capecitabine plus temozolomide, lu-177 DOTATATE, telotristat with a SSRA, Y-90 microspheres, placebo and/or standard of care.

Cabozantinib (Cabometyx) was previously reviewed by CDA-AMC as monotherapy for treating adults with locally advanced or metastatic differentiated thyroid carcinoma and it was recommended for reimbursement with clinical criteria and/or conditions in November 2022.[2] Additionally, in combination with nivolumab, it was recommended for reimbursement also with clinical criteria and/or conditions for treating adults with advanced or metastatic renal cell carcinoma who had no prior systemic therapy for metastatic disease in November 2023.[3]

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Cabozantinib, oral tablets (60 mg, 40 mg or 20 mg)
Relevant Health Canada indication	No indication for neuroendocrine tumours.
Mechanism of action	Cabozantinib inhibits multiple receptor tyrosine kinases, including AXL, FLT3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, TYRO3, and VEGF, which are involved in cell proliferation and angiogenesis.
Recommended dosage	NA
Data protection status	2027
Status of generic drugs / biosimilars	Two generics are under review by Health Canada
Information on the CDA-AMC review	
Requester	Oncology Working Group
Indication under consideration for reimbursement	Adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy.

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-sponsored Reimbursement Review. We received 1 patient group submission from Canadian Neuroendocrine Tumour Society (CNETS) and 1 clinician group submission from the Commonwealth Neuroendocrine Tumour Research Collaborative (CommNETs), Canadian members. CNETS summarised patient input data and provided evidence on patients' experiences and perspectives of living with neuroendocrine cancer, including the Global NET Patient Survey (2017) by the International Neuroendocrine Cancer Alliance,[4] the NET Patient Experiences and Perspectives Survey (2022) conducted online via SurveyMonkey, and qualitative interviews with NET patients and caregivers who

have experience with cabozantinib. Several clinical experts provided input to support the review. The full submissions received are available on the project landing page in the consolidated input document <insert hyperlink or citation to project landing page>.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two oncologists with expertise in the diagnosis and management of epNET and pNET participated as part of the review team, with representation from Ontario and Manitoba, Canada.

Disease Background

Neuroendocrine tumors (NETs) are a diverse group of cancers originating from the secretory cells of the diffuse neuroendocrine system.[5] Pancreatic neuroendocrine tumors (pNETs) are a subset of gastroenteropancreatic NETs and arise in the endocrine tissues of the pancreas.[6] Extra-pancreatic NET (epNETs) can occur in various organs such as the stomach, intestines, lungs, and esophagus.[1] These tumors can be nonfunctional (i.e., unassociated with a hormonal syndrome) or functional (i.e., producing hormones that cause various clinical symptoms).[1,6] NETs often are nonfunctional and present with nonspecific symptoms, leading to delays in diagnosis.[7] A retrospective study in Ontario found that 20.8% of NETs patients presented with metastatic disease at diagnosis.[8]

According to the input from the clinician group, NETs are one of the fastest growing classes of cancers in Canada and worldwide. In Canada, an Ontario-based study reported an increase in incidence from 2.46 per 100,000 to 5.86 per 100,000 over 15 years from 1994 to 2009, with pancreatic NETs (pNETs) accounting for about 10% of cases.[8] The estimated overall survival (OS) rates for patients with NETs are 68.3% at 3 years, 61.0% at 5 years, and 46.5% at 10 years.[8] The primary tumor site and disease stage at diagnosis significantly affect OS. For non-metastatic disease, the 10-year OS rate is 68.2%, while it is 17.5% for those with metastases at presentation and 18.7% for metastases after the initial diagnosis.[8] For pNETs patients, the estimated 10-year OS is about 30%.[8] A collaborative team of experienced healthcare practitioners is essential for diagnosing and managing NETs. Diagnosis typically involves specialized pathological testing, imaging, and biochemical tests to confirm, categorize, and stage the disease.

According to the patient input for this review, NETs significantly negatively impact patients' quality of life (QoL), causing symptoms like fatigue, diarrhea, and pain, which affect daily activities, emotional health, social life, and ability to work. Patients often experience a substantial negative impact on their energy, overall well-being and require various treatments to manage symptoms and disease progression.

Current Management

Treatment Goals

Per the input from the clinician group, current treatment goals for patients with locally advanced or metastatic epNET or pNET are to prolong life, delay disease progression, reduce cancer-related symptoms, prevent treatment complications, and to improve or maintain patients' functioning and QoL.

Given these treatment goals, clinical experts consulted by CDA-AMC emphasized that progression-free survival (PFS) and health-related quality of life (HRQoL) are the most important outcomes for patients with NETs. They noted that the objective response rate is less relevant, as HRQoL captures this measure. The experts indicated that assessing overall OS may be more challenging due to the protracted disease course, cross-over between intervention and comparator groups, and small sample sizes in a trial setting.

Current Treatment Options

For locally advanced or metastatic epNET or pNET, treatment approaches vary based on tumour grade, differentiation, functionality, and the extent and location of the disease.[9] According to the input from the clinician group, treatment options include surgical resection, intraarterial hepatic therapy, and systemic therapy options including targeted agents, peptide receptor radionuclide therapy (PRRT), and chemotherapy when necessary. For localized solid tumors, surgery is typically the first-line treatment. For patients with metastatic disease, systemic drug therapies are used. Somatostatin analogues (SSAs) are generally the initial therapy for patients with unresectable metastatic disease or hormonal overproduction syndromes. For those who have progressed while on SSAs, treatment options include targeted agents like everolimus, sunitinib and cabozantinib, chemotherapy such as capecitabine plus temozolomide (CAPTEM), lu-177 DOTATATE, or PRRT for NETs that have advanced after first-line SSA therapy.

Key characteristics of cabozantinib are summarized with other treatments available for locally advanced or metastatic epNET or pNET in the Supplemental Material document, in the Key Characteristics Table 1 in Appendix 1.

Unmet Needs and Existing Challenges

Canadian members of CommNETs reported that all patients with NETs eventually progress, developing metastases in multiple organ systems, which ultimately leads to death. However, there is generally a considerable period during which novel therapies can be applied. Current treatments are not effective or available for all patients, are poorly tolerated, and can lead to drug resistance. For example, PRRT is not universally funded for all NET patients across Canada, creating issues of inequity. Where funded, PRRT is available only at selected centers, requiring patients to travel, which negatively impacts the QoL for both patients and caregivers. Additionally, PRRT and chemotherapy regimens (e.g., CAPTEM) are associated with an increased risk of myelodysplastic syndromes and acute myeloid leukemia. Thus, there is a need for additional safe and effective treatment options for patients who have progressed or are unsuitable for current treatments to improve overall survival, slow disease progression, and control hormonal symptoms.

Clinical experts also noted that all patients will eventually progress. Current treatments, such as SSRAs and Lu-177, are not particularly effective and have significant side effects, highlighting a substantial unmet need for effective and well-tolerated treatment options in this patient population.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Potential Place in Therapy

Cabozantinib is an oral small-molecule inhibitor of multiple tyrosine kinase inhibitors, including VEGF receptors, MET, AXL, and RET. This mechanism differs from other treatment options. Angiogenesis plays a key role in the pathogenesis of NETs. Experts highlighted that cabozantinib, as a multiple antiangiogenic agent, could potentially address the underlying disease process, improve patients' quality of life, and shift the current treatment paradigm for NETs, reducing the use of everolimus.

The clinician group agreed with the experts that cabozantinib would be an option for patients with advanced epNET or pNETs who have received at least one prior therapy. They highlighted that it could become the standard of care for this population. In the pNETs population, cabozantinib will replace the current use of everolimus or sunitinib in second-line treatment or in place of best supportive care. Given the limited funded treatment options for the epNETs population, cabozantinib will replace the use of best supportive care.

Patient Population

Clinical experts consulted for this review consider adults with locally advanced or metastatic ep-NET or p-NET who have experienced disease progression after at least one prior treatment or who are intolerant of the other therapies to be the most suited

for cabozantinib treatment. The prior treatments include but are not limited to SSRA, lu-177 DOTATATE, or everolimus. Eligible patients also include those who are intolerant to the first-line treatments. Clinical experts highlighted that everolimus is not well tolerated, with side effects including hyperglycemia, pneumonitis and other infections. Physician judgments, examinations, and diagnostic imaging (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]) are needed to assess disease progression. No companion test is required for initial cabozantinib treatment, and all patient groups are expected to benefit from cabozantinib, with no expected subgroup effects.

The clinician group agreed with the experts that the patient population best suited for cabozantinib should follow the eligibility criteria of the CABINET study.[10] Cabozantinib is considered an additional line of treatment after progression on PRRT, sunitinib, or everolimus in pNET and GINET, and after everolimus for lung NETs. No patient populations are expected to be unsuitable for treatment. The clinician group also agrees that no specific diagnostic tests are required to initiate cabozantinib treatment.

Assessing the Response to Treatment

According to the clinical experts consulted for this review, patients undergoing treatment with cabozantinib may be assessed for treatment response via routine medical imaging every 2 to 3 months and routine clinical examination or blood work every month. The clinical experts consider clinically meaningful responses to include clinical and radiographic evidence of disease stability or progression, the maintenance or improvement of symptoms and HRQoL.

The clinician group agrees with the clinical experts that clinical assessments (such as symptoms, QoL, or disease bulk) and radiographic information (size of lesions) should be used to evaluate patients' responses to treatment.

Discontinuing Treatment

Treatment with cabozantinib would be discontinued due to evidence of disease progression based on RECIST criteria, intolerable toxicities (e.g., fatigue, diarrhea, hypertension, weight loss, stomatitis, hand-food syndrome, decreased appetite), or if radiation or surgery is required, according to the clinical experts.

The clinical group agreed with the experts that they would discontinue cabozantinib treatment if the disease progressed or the toxicity became unacceptable. The clinical group also pointed out patient preference might be a reason for discontinuing cabozantinib.

Prescribing Considerations

The clinical experts consulted for this review expressed that the initial cabozantinib prescription should be prescribed by clinicians with expertise in the management of NETs (e.g., medical oncologists or surgical oncologists), and cabozantinib can be given in community settings.

The clinician group indicated that a collaborative team of healthcare providers experienced in managing NETs may be needed to manage and follow up on cabozantinib treatment. An oncologist-led multidisciplinary team may support using cabozantinib in the community setting and provide follow-up care.

Additional Considerations

The clinical experts consulted for this review noted that in their experience cabozantinib is better tolerated than other treatment options in this patient population.

Clinical Review

Methods

We conducted a systematic review to identify evidence for cabozantinib in the treatment of adults with locally advanced or metastatic epNET or pNET who have received at least 1 prior therapy (including but not limited to everolimus). Studies were selected according to the eligibility criteria in Table 2. We also considered long-term extension (LTE) studies of included RCTs, indirect treatment comparisons (ITCs) that adhered to the eligibility criteria except for the study design criteria, and studies addressing gaps that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We included placebo as one of the relevant comparators because our preliminary scoping indicated that evidence comparing active treatments might not be available. Clinical experts also noted that treatment options are limited for patients with progressive NETs, especially for those with pNET, after several prior treatments. We selected outcomes (and follow-up times) for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations.

An information specialist conducted a literature search of key bibliographic databases, trial registries, and grey literature sources, using a peer-reviewed search strategy. The initial search was completed on March 5, 2025 with alerts maintained until the Formulary Management Expert Committee (FMEC) meeting on July 17, 2025. See the Supplemental Materials document for detailed search strategies.

Detailed methods for literature searches, study selection, data extraction, and risk of bias appraisal are in the Supplemental Material in Appendix 2.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adult patients with locally advanced or metastatic epNET or pNET who have received at least 1 prior therapy
Intervention	Cabozantinib
Comparator	• Somatostatin analogs: lanreotide or octreotide • Everolimus • Sunitinib • Streptozocin/doxorubicin/5-fluorouracil • Capecitabine/temozolomide • Lu-177 DOTATATE • Telotristat with a SSRA • Y-90 microspheres • Placebo and/or standard of care
Outcomes	Efficacy: • Progression-free survival • HRQoL • Overall survival Safety: • AE

	• SAEs • WDAEs • Death due to AE
Study design	Phase 3 and 4 RCTs

AE = adverse events; HRQoL = Health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawals due to adverse events

Note: Although medullary thyroid carcinoma and small cell lung carcinoma are both neuroendocrine carcinomas, they are managed differently in clinical practice. Therefore, we excluded studies that focus on these two diseases.

Clinical Evidence

From the search for primary studies, we identified 218 unique records via the searches of databases and registers, of which we excluded 216 by title and abstract. We screened 2 records by full text and included 1 report of 1 study (the CABINET trial).[10] We did not identify any potentially relevant records via other sources. No reports of long-term extensions of the included studies or studies addressing gaps were identified.

From the search for ITCs, we identified 118 unique records via the searches of databases, of which we excluded 115 by title and abstract. We screened 3 records by full text, of which none met the eligibility criteria by full-text screening. We did not identify any potentially relevant records via other sources.

A list of excluded studies, including reasons for exclusion, is in the Supplemental Material document in Appendix 2.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the included study (CABINET) are summarized below. Additional details regarding the inclusion and exclusion criteria, interventions and comparators, and relevant outcome measures, are in the Supplemental Material document in Appendix 3.

The CABINET trial by Chan et al. (2025)[10] is a multicenter, phase 3, double-blind (outcome accessors and participants), randomized controlled trial funded by the National Cancer Institute and Exelixis (the manufacturer), with additional support from the Alliance for Clinical Trials in Oncology and Alliance Foundation Trials programs (https://acknowledgments.alliancefound.org). The trial was conducted at 62 sites in the United States, with no sites in Canada.[10] The trial aimed to evaluate the efficacy and safety of cabozantinib in adult patients with previously treated, progressive advanced epNETs or pNETS.

The CABINET trial[10] included patients aged 18 or older with histologically confirmed, locally advanced, or metastatic well- or moderately differentiated neuroendocrine tumors (epNETs or pNETs). Eligible patients had WHO tumor grades of 1 to 3 and an ECOG performance-status score of 0 to 2. They must have experienced disease progression (per RECIST 1.1 criteria) within 12 months before enrollment or unacceptable side effects after at least one FDA-approved therapy. The original protocol required that patients had prior therapy with everolimus, but a later amendment expanded the list of potential prior therapies owing to changes in the treatment landscape. These included somatostatin analogues, Lu-177 dotatate, everolimus, temozolomide (with or without capecitabine), cisplatin or carboplatin plus etoposide (for epNET), and sunitinib (for pNET). Patients with poorly differentiated neuroendocrine carcinoma and high-grade neuroendocrine carcinoma without specified differentiation status were excluded.[10] The inclusion and exclusion criteria were consistent across the two cohorts, focusing on patients with progressive disease despite prior therapies.[10]

The trial enrolled 298 patients, including 203 with epNETs and 95 with pNETs.[10] Patients were randomly assigned in a 2:1 ratio to receive either 60 mg of cabozantinib or placebo orally daily. Randomization was stratified based on concurrent somatostatin analogue use and primary tumor site (midgut gastrointestinal and unknown primary vs. nonmidgut gastrointestinal, lung, or other

sites) for the epNET cohort, and concurrent somatostatin analogue use and previous sunitinib therapy for the pNET cohort.[10] To manage adverse events, treatment interruption and dose reduction for cabozantinib (to 40 mg, then to 20 mg) and placebo were permitted.[10] Participants can continue using somatostatin analogs if their dose has been stable for at least 2 months before enrollment. However, participants are prohibited from using full-dose oral anticoagulation and antiplatelet treatments, strong CYP3A4 inhibitors or inducers. Considering the impact of cabozantinib on the QTc interval, drugs that prolong the QTc interval should be avoided if possible. Patients were unaware of their assigned treatment until disease progression, unacceptable toxic effects, or withdrawal of consent. In November 2020, a protocol amendment allowed patients receiving placebo to cross over to open-label cabozantinib after centrally confirmed progressive disease.[10]

There was no specific run-in period mentioned in the trial design.[10] The trial was terminated early based on interim analysis results showing PFS benefit, with the data-cutoff date for the final analyses being August 24, 2023.[10] The primary endpoint was PFS, defined as the time from randomization to radiographic progressive disease (RECIST 1.1 by the investigator and confirmed in real time by blinded independent central review) or all-cause death. Patients were censored if they did not have post-baseline assessments, started new anti-cancer therapy before progression, were lost to follow-up, or reached the data cut-off without experiencing a PFS event. To evaluate tumor response and progression, participants underwent radiographic imaging every 12 weeks. Secondary endpoints of relevance included overall survival, defined as the time from randomization to death from any cause, and safety, measured by adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Patients without an OS event were censored at the date that they were last known to be alive. An optional correlative study also assessed the HRQoL using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Quality of Life-gastrointestinal-related neuroendocrine tumors 21, but the results have not yet been available.

Statistical Testing and Analysis Populations

The calculated sample size (210 for epNET, 185 for pNET) aimed to provide the trial with 90% power to detect a true hazard ratio (HR) for primary endpoint, PFS, of 0.583 in the epNET cohort and 0.568 in the pNET cohort.[10] This was based on a stratified one-sided log-rank test with an overall significance level of 0.025, corresponding to a two-sided significance level of 0.05. For time-to-event analyses, the target sample size was event-driven. The trial required 164 progression events in the epNET cohort and 149 progression events in the pNET cohort.[10]

The trial included two interim analyses for futility after 33% and 66% of the projected progression events occurred in each cohort.[10] For each interim analysis, one-sided alpha spending of 0.001 for efficacy (PFS testing) was applied to control the type I error rate at a one-sided alpha of 0.025. Other end points were uncontrolled for multiplicity and HRQoL was not inferentially tested. P-values reported herein are two-sided. In May 2023, the study investigators conducted protocol-specified interim analyses of PFS (second interim analysis for epNET cohort, first interim analysis for pNET cohort) using local investigator assessment, followed by a blinded independent central review. Based on these interim results, the data and safety monitoring board recommended early trial termination. On August 24, 2023, the trial group assignments were unblinded, allowing all patients in the placebo group to receive cabozantinib. The trial used this time point as the data-cutoff for the final analyses. The trial also conducted a prespecified OS analysis.

Efficacy analyses followed the intention-to-treat (ITT) principle, including all randomized patients in the analysis. Patients were assigned to the treatment group they were randomized to, regardless of the actual treatment received. Safety analyses were based on the safety population, which included patients who were randomized and received any amount of protocol therapy. In the epNET cohort, the safety population had 2 fewer participants than the ITT population in each group. In the pNET cohort, the safety population had 1 fewer participant than the ITT population in the cabozantinib group and was the same as the ITT population in the placebo group.

Patient Disposition

Table 3 presents patient disposition of the CABINET trial.[10]

Between October 2018 and August 2023, 203 patients with epNET (cabozantinib: 134, placebo: 69) and 95 patients with pNET (cabozantinib: 64, placebo: 31) were randomly assigned to receive cabozantinib or placebo.[10] The ITT population included several misallocated patients: the epNET cohort had 7 patients with pNET (4 in the cabozantinib group and 3 in the placebo group), and the

pNET cohort had 3 patients with epNET (2 in the cabozantinib group and 1 in the placebo group). Disease progression was the most common reason for discontinuing the assigned regimen in both the cabozantinib and placebo groups.[10]

Table 3: Patient Disposition in the Intent-to-Treat population

Status, n (%)	EpNET cohort (n= 203)		pNET cohort (n= 95)	
	Cabozantinib, n	Placebo, n	Cabozantinib, n	Placebo, n
Eligible patients randomized	134	69	64	31
Initiated treatment (Safety population)	132	67	63	31
Treatment discontinuation (% of eligible patients)*	111 (83)	60 (87)	49 (77)	29 (94)
Reason for treatment discontinuation, n (% of randomized patients)				
• Progression	52 (39)	38 (55)	28 (44)	23 (74)
• AE	34 (25)	9 (13)	10 (16)	0
• Withdrawn consent	7 (5)	4 (6)	5 (8)	4 (13)
• Death	6 (4)	4 (6)	0	0
• Other reason	6 (4)	3 (4)	3 (5)	2 (6)
• Alternative treatment	5 (4)	1 (1)	1 (2)	0
• Other disease	1 (1)	1 (1)	2 (3)	0

AE = adverse event; epNET= extra-pancreatic neuroendocrine tumors; pNET=pancreatic neuroendocrine tumors.

*The reasons for discontinuation of the study were not clearly reported, except in cases where patients withdrew consent.

Source: Supplementary Appendix of Chan et al. (2025)[10]

Baseline Characteristics

In the epNET cohort, the median age was 66 years in both cabozantinib (range: 28-86 years) and placebo groups (range: 30-82 years), with about 50% of the female sex.[10] Most patients (63% in the cabozantinib group and 52% in the placebo group) had an ECOG performance-status score of 1, indicating mild symptoms but ambulatory. Primary tumour sites were mainly gastrointestinal (52% in the cabozantinib group and 67% in the placebo group) and lung (20% in the cabozantinib group and 17% in the placebo group), with 16% in the cabozantinib group and 3% in the placebo group having unknown primary sites. Most patients (64% in the cabozantinib group and 70% in the placebo group) had grade 2 tumours, and 31% in the cabozantinib group and 36% in the placebo group had functional tumours causing hormone syndromes. Nearly all patients (93% in both groups) had previously received somatostatin analogues, and a substantial portion had undergone peptide receptor radionuclide therapy with Lu-177 dotatate (60% in the cabozantinib group and 59% in the placebo group) and everolimus (72% in the cabozantinib group and 64% in the placebo group).

In the pNET cohort, the median age was 60 years in the cabozantinib group (range: 29-79 years) and 64 years in the placebo group (range: 39-79 years), with 42% of the female sex.[10] A higher percentage of patients (55% in the cabozantinib group and 48% in the placebo group) had an ECOG performance status score of 0, indicating full activity without symptoms. Most patients (61% in both groups) had grade 2 tumours, 17% in the cabozantinib group and 16% in the placebo group had functional tumours. Nearly all patients (98% in the cabozantinib group and 97% in the placebo group) had received somatostatin analogues, and many had been treated with Lu-177 dotatate (59% in the cabozantinib group and 58% in the placebo group), everolimus (80% in the cabozantinib group and 81% in the placebo group), and temozolomide-based therapy (67% in the cabozantinib group and 52% in the placebo group). Additionally, 28% of patients in the cabozantinib group and 22% in the placebo group had previously received sunitinib.

Table 4 of Appendix 4 presents additional baseline demographics and disease characteristics from the CABINET trial.[10]

Treatment Exposure and Concomitant Medications

In the epNET cohort, among the safety population, the median duration of cabozantinib treatment (n=132) was 5.5 months, ranging from 0.2 to 32.4 months. Dose reductions due to adverse events occurred in 66% of patients, with a median daily dose of 38.4 mg. For the placebo group (n=67), the median duration was 2.8 months, ranging from 0.6 to 21.4 months. Dose reductions due to adverse events occurred in 10% of patients, with a median daily dose of 59.0 mg. In the cabozantinib group, 45% of patients received subsequent anticancer therapy, while 67% of patients in the placebo group (including 20 [33%] who crossed over to open-label cabozantinib) received additional treatment (details in Supplementary Table 4 of Chen et al. 2025).[10] More patients in the cabozantinib group (55%) received no additional therapy than in the placebo group (33%).

In the pNET cohort, among the safety population, the median duration of cabozantinib treatment (n=63) was 8.3 months, ranging from 0.5 to 39.6 months. Dose reductions due to adverse events occurred in 68% of patients, with a median daily dose of 37.9 mg. For the placebo group (n=31), the median duration was 2.9 months, ranging from 0.5 to 11.2 months. Dose reductions due to adverse events occurred in 19% of patients, with a median daily dose of 56.9 mg. In the cabozantinib group, 51% of patients received subsequent anticancer therapy, compared to 62% in the placebo group (including 12 [41%] who crossed over to open-label cabozantinib) (details in Supplementary Table 5 of Chen et al. 2025).[10] More patients in the cabozantinib group (49%) of those in received no additional therapy than in the placebo group (38%).

More details on concomitant medications, including the timing of its initiation, were not provided.

Critical Appraisal

Table 9 of Appendix 5 in the Supplementary Material document presents the results of the risk of bias appraisal of the included study.

Internal Validity

The CABINET trial protocol indicated that a randomization system was used to performed stratified permuted block randomization, suggesting a low risk of bias in the randomization process, though specific details of allocation concealment were unclear. Patient characteristics at baseline were relatively balanced in both the epNET and pNET cohorts, except the cabozantinib group had a higher unknown primary tumor site in the epNET cohort. This may be attributable to chance given the relatively small sample size. Clinical experts consulted by the review team did not expect an important impact of this imbalance on efficacy. The targeted sample sizes were 210 participants (164 events) for the epNET cohort and 185 participants (149 events) for the pNET cohort. However, the actual sample sizes were 203 participants (111 events) for the epNET cohort and 95 participants (57 events) for the pNET cohort, which is smaller than the targeted sample sizes or events, particularly for the pNET cohort. Despite not achieving the planned sample size, the trial had enough power to detect statistical differences between the two groups for PFS outcome. The small number of participants or events, particularly in the pNET cohort, could be associated with unstable treatment effect estimation in the analyses.

Although the trial was double-blind, the blinding process description was not fully explicit. Based on the publication, patients were blinded and the outcome assessor was likely blinded before the data cutoff date. Given that cabozantinib is linked to specific AEs like hypertension and diarrhea, this could potentially unblind patients and investigators. This potential for unblinding might influence subjective components of disease progression assessments (e.g., when doing the clinical evaluations and assessing the tumour size through measuring lesion size from medical imaging) and adverse event reporting, potentially biasing treatment efficacy and safety estimates. However, there is not clear evidence of unblinding and use of a blinded independent central review for PFS assessments enhanced the result's internal validity. The trial presents treatment-related adverse events (AEs) rather than all AEs, which involves subjective interpretations of AE attribution by the investigator. There was no statement in the protocol about whether attribution occurred in a blinded manner.

The primary analyses (PFS and OS) were based on the intention-to-treat (ITT) population, which is appropriate.[10] In this trial, most patients discontinued the intervention (cabozantinib or placebo) due to disease progression or adverse events, which aligns with clinical practice. The proportion of discontinuation of study treatment due to withdrawn consent (suggestive of trial discontinuation)

or unknown reasons was small and similar between the two groups (Table 4). The trial's statistical methods were generally appropriate, using stratified Cox regression models and Kaplan-Meier methods for PFS and overall survival analysis. Since the trial did not report the results of testing the proportional hazards assumption, the validity of the assumption underlying the hazard ratios from time-to-event analyses could not be comprehensively assessed.[11] Visual inspection of the Kaplan-Meier plots suggests the assumption was likely met for PFS in both cohorts (Figures 1 and 2). However, Kaplan-Meier plots for overall survival did not separate at any point during follow-up (Figures 1 and 2). While the trial adjusted for multiplicity in the planned interim analysis for the primary outcome (i.e., PFS), it did not appear that adjustments were made for secondary outcomes (i.e., OS), however, these were not statistically significant. HRQoL was not tested statistically. The duration of follow-up was adequate to capture the benefit for PFS, although less so for OS or long-term safety outcomes. The trial relied on relative hazard estimations and medians (between-group difference not reported), without providing absolute risk estimations at relevant time points between the two groups to assist in further judging the clinical importance of time-to-event results.

In this trial, the epNET cohort included 7 patients with pNET (4 in the cabozantinib group and 3 in the placebo group), and the pNET cohort included 3 patients with epNET (2 in the cabozantinib group and 1 in the placebo group).[10] Misallocating patients to incorrect cohorts could introduce bias, potentially skewing results. However, sensitivity analyses excluding these misallocated participants yielded consistent results with the primary analyses (Table 7 of Appendix 4).

Ending the trial early based on interim analysis results (second interim analysis for epNETs and first interim analysis for pNET) and the superior efficacy observed with cabozantinib could potentially overestimate the treatment effect.[10,12] This decision might prevent the trial from assessing potential long-term benefits and fully capturing adverse effects. The trial's power calculations were based on the primary endpoint (PFS),[10] and findings regarding secondary endpoints (e.g., OS) may be underpowered. Allowing patients who received a placebo to crossover to the cabozantinib group is an important ethical consideration, but the crossover (20 in the epNET cohort and 12 in the pNET cohort) may diminish the ability to observe an OS benefit for cabozantinib in both cohorts. Participants in the placebo group who experienced disease progression and crossed over to open-label cabozantinib could influence HRQoL assessments and self-reported adverse events.

The CABINET trial did not provide details on the proportion of patients who discontinued the trial nor censoring reasons for time-to-event end points. Therefore, we are unclear about how many patients might have been censored due to loss to follow-up or for moving to subsequent treatment before disease progression. Based on the provided disposition, this number appears to be low, but we cannot make a definitive conclusion about this for PFS, OS, and harm outcomes. The number of patients contributing data decreases substantially over time for HRQoL. The analysis of complete cases assumes that missing values occurred completely at random, which is not a reasonable assumption given the likely reasons for missing values (e.g., death).

Although the CABINET trial used PFS to assess the efficacy of cabozantinib as the primary outcome, the validity of PFS as a surrogate endpoint to predict an OS benefit among patients with NETs remains uncertain. One study using observational data reported that PFS was associated with improved OS among patients with metastatic NETs who received somatostatin analogs or everolimus.[13] However, trial-based evidence specific to the treatment regimen of interest is not available.

External Validity

The CABINET trial included patients with histologically confirmed, locally advanced or metastatic well or moderately differentiated epNET or pNET.[10] The trial included a well-defined patient population with clear inclusion and exclusion criteria, ensuring the findings' applicability to the broader NET patient population.[10] Patients with poor ECOG performance status (scores of 3 or higher) and those with poorly differentiated neuroendocrine carcinoma were not eligible, which may limit generalizability to patients with poorer performance status or more aggressive disease.

The trial was conducted at 62 sites in the United States.[10] The trial authors stated that the demographic characteristics of the trial participants are representative and generalizable to those with neuroendocrine tumors in the United States and elsewhere,[10] the mean age and sex were similar to a study conducted in Ontario in 2015.[8] However, the trial participants may not fully represent the ethnic and demographic diversity seen in Canadian clinical practice or differ from Canadian medical centers in terms of access to supportive medications and procedures.

The trial used placebo as the comparator,[10] which may not fully reflect Canadian clinical practice where active comparators such as everolimus or Lu-177 dotatate are commonly used. The clinical experts consulted by the review team indicated that the choice of placebo was justified due to the lack of established efficacy of other therapies in patients with progressive disease, particularly for the epNET cohort. However, concerns arose for patients with pNET, as they have more treatment options than those with epNET. We did not identify any studies comparing the efficacy and safety of cabozantinib and other active comparators.

The CABINET trial Included patients who had treatments like PRRT, Lu-177 dotatate, everolimus, and targeted therapies or allowing co-interventions such as somatostatin analogues,[10] aligns well with Canadian treatment practices, enhancing the results' generalizability in Canadian settings. The trial did not use specific inclusion criteria, such as randomizing only patients who tolerated or adhered to treatment, enhancing generalizability to the wider patient population. In the trial, patients received regular monitoring and dose adjustments, which aligned with routine practice in Canada, according to clinical experts. In addition, cabozantinib was administered after progression on prior therapies and at a dose of 60 mg orally daily with dose reductions specified for managing adverse events, which are appropriate and align with its use in Canadian clinical practice, where dose adjustments are made based on patient tolerance. Given that cabozantinib is used similarly for other indications, the intervention has good applicability to Canadian practice.

The primary outcome of PFS and secondary outcomes such as OS and safety outcomes in the trial[10] are clinically relevant and important to patients. These outcomes reflect measures of both efficacy and harms, and the methods used for assessing these outcomes (e.g., RECIST 1.1 criteria) align with clinical practice in Canada. Due to the lack of formal statistical comparisons and the high risk of bias in HRQoL data, we cannot draw any definitive conclusions on this patient-important outcome.

Results

Efficacy

Table 4 presents the results for outcomes important to this review. The results of sensitivity analyses for efficacy outcomes show consistent results with the primary analyses. Figure 1 and Figure 2 present the Kaplan-Meier plots for PFS and OS in the epNET and pNET cohorts. Key results include the following:

- **PFS:** Compared to placebo, cabozantinib was associated with a HR of 0.38 (95% CI, 0.25 to 0.59) for disease progression or death in the epNET cohort and a HR of 0.23 (95% CI, 0.12 to 0.42) in the pNET cohort. [10]

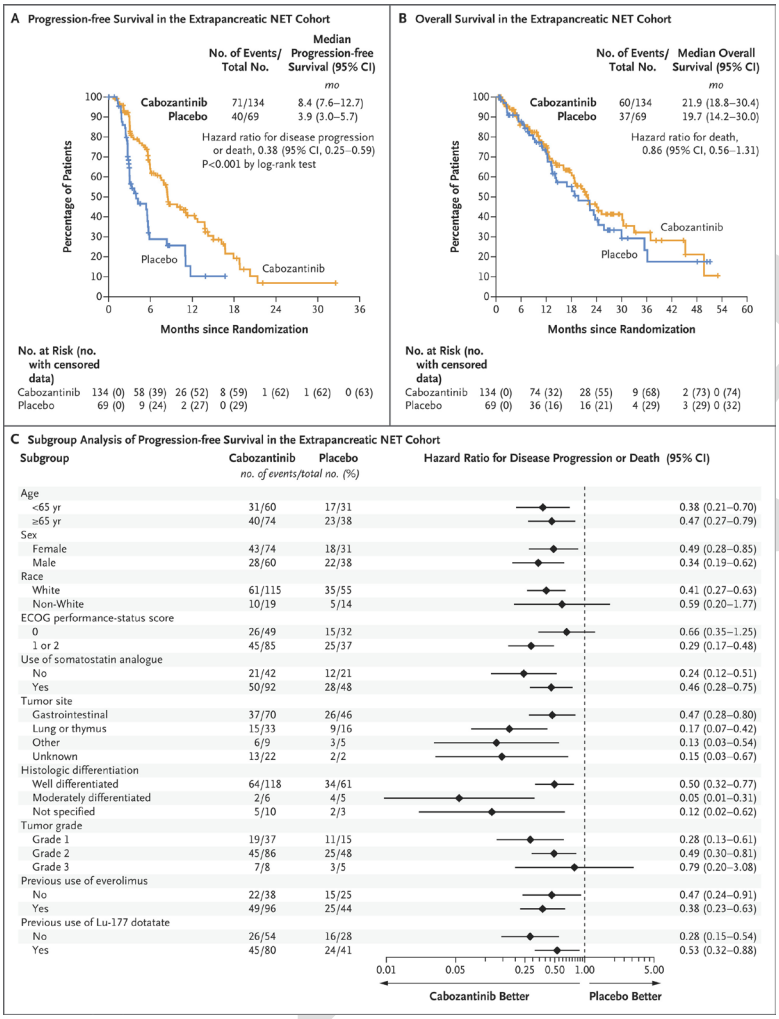
- **OS:** The evidence was insufficient to show meaningful differences between the cabozantinib and placebo groups in both the epNET and pNET cohorts. The 95% CIs were wide and overlapped with the null threshold (i.e., HR = 1) in both the epNET and pNET cohorts, with the pNET cohort having a particularly wide 95% CI.[10]

- **HRQoL**: The overall HRQoL remained stable over time among participants who completed the EORTC QLQ-C30 questionnaire and seemed comparable between the two groups in both the epNET and pNET cohorts. However, the 95% CIs were wide and overlapping for the two groups, based on descriptive mean scores and 95% CIs.[10] Formal analyses for HRQoL have not been reported in the included study.

- **Sensitivity analyses**: The trial conducted sensitivity analyses, including PFS as assessed by investigators, accounting for the misallocation of patients into the incorrect disease cohort.[10] These analyses yielded consistent results with the primary analysis in both the epNET and pNET cohorts.

Figure 1: PFS and OS in epNET cohorts

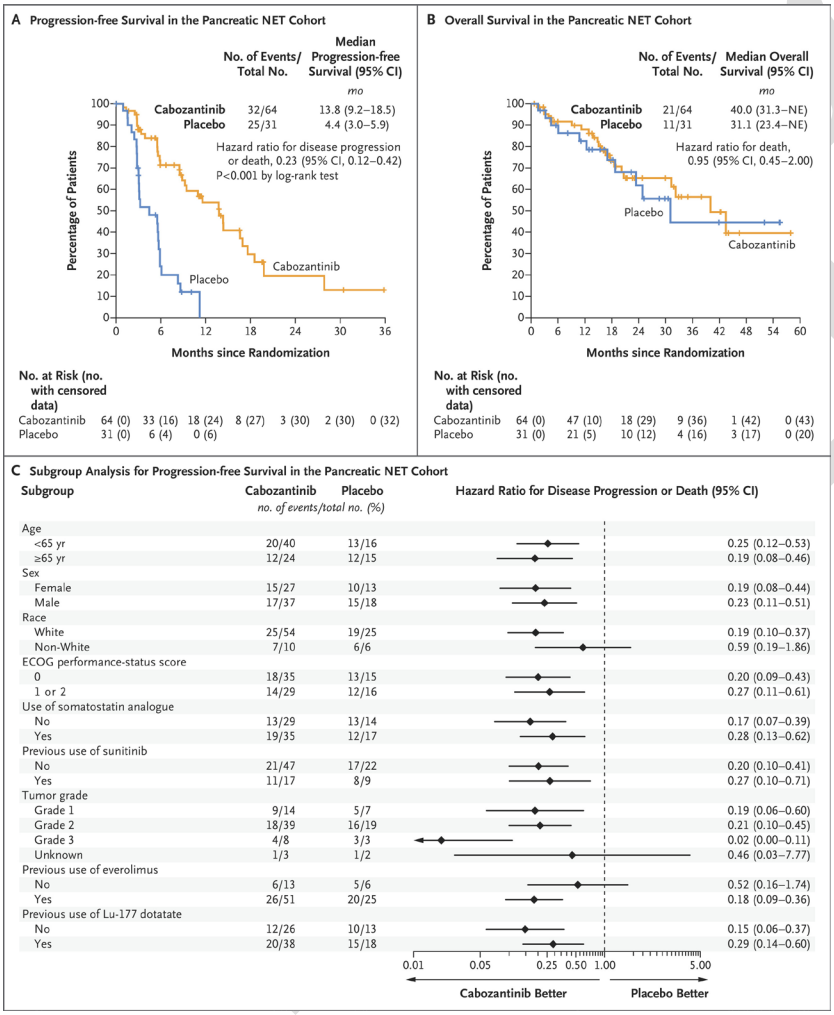
Panel A shows progression-free survival, as assessed retrospectively by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (two-sided stratified log-rank P<0.001 for the comparison between the cabozantinib and placebo groups), among patients in the extrapancreatic neuroendocrine tumors cohort, and Panel B shows overall survival. Panel C shows progression-free survival according to stratification factors and selected clinical subgroups of patients in the extrapancreatic neuroendocrine tumors cohort. For the subgroup analysis of tumor grade, the "unknown" subgroup is not shown, owing to there having been no progression events in either the cabozantinib group or the placebo group. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers reflecting greater disability.



Source: From [N Engl J Med, Chan JA, Geyer S, Zemla T, Knopp MV, Behr S, Pulsipher S, Ou FS, Dueck AC, Acoba J, Shergill A, Wolin EM, Halfdanarson TR, Konda B, Trikalinos NA, Tawfik B, Raj N, Shaheen S, Vijayvergia N, Dasari A, Strosberg JR, Kohn EC, Kulke MH, O'Reilly EM, Meyerhardt JA., Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors, 392(7), 653-665. Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[10]

Figure 2: PFS and OS in pNET cohorts

Panel A shows progression-free survival, as assessed retrospectively by blinded independent central review according to RECIST 1.1 (two-sided stratified log-rank P<0.001 for the comparison between the cabozantinib and placebo groups), among patients in the pancreatic neuroendocrine tumors cohort, and Panel B shows overall survival. Panel C shows progression-free survival according to stratification factors and selected clinical subgroups of patients in the pancreatic neuroendocrine tumors cohort. The subgroup analysis of histologic differentiations is not shown because there were no progression events in either the cabozantinib group or the placebo group in the “moderately differentiated” and the “not specified” subgroups.



Source: From [N Engl J Med, Chan JA, Geyer S, Zemla T, Knopp MV, Behr S, Pulsipher S, Ou FS, Dueck AC, Acoba J, Shergill A, Wolin EM, Halfdanarson TR, Konda B, Trikalinos NA, Tawfik B, Raj N, Shaheen S, Vijayvergia N, Dasari A, Strosberg JR, Kohn EC, Kulke MH, O'Reilly EM, Meyerhardt JA., Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors, 392(7), 653-665. Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[10]

Table 4: Summary of Key Efficacy Results Patient Disposition in the Intent-to-Treat population

Variable	epNET cohort (n= 203)		pNET cohort (n= 95)	
	Cabozantinib, n=134	Placebo, n=69	Cabozantinib, n=64	Placebo, n=31
PFS*				
Patients with disease progression or death, n (%)	71 (53)	40 (58)	32 (50)	25 (81)
Median (95% CI) time to event, months	8.4 (7.6 to 12.7)	3.9 (3.0 to 5.7)	13.8 (9.2 to 18.5)	4.4 (3.0 to 5.9)
Hazard ratio (95% CI)	0.38 (0.25 to 0.59)	Reference	0.23 (0.12 to 0.42)	Reference
P value	<0.001	Reference	<0.001	Reference
Median follow-up, months, (95% CI)	10.2 (8.2 to 13.8)		13.8 (10.1 to 19.7)	
OS**				
Patients who died, n (%)	60 (45)	37 (54)	21 (33)	11 (35)
Median (95% CI) time to event	21.9 (18.8 to 30.4)	19.7 (14.2 to 30.0)	40.0 (31.3 to NE)	31.1 (23.4 to NE)
Hazard ratio (95% CI)	0.86 (0.56 to 1.31)	Reference	0.95 (0.45 to 2.00)	Reference
P-value	NR	Reference	NR	Reference
Median follow-up, months, (95% CI)	24.2 (NR)		23.1 (NR)	
HRQoL***				
Descriptive results	The trial authors concluded that the overall HRQoL remained stable over time and was similar between the two groups in both cohorts.			

CI = confidence interval; epNET = extrapancreatic neuroendocrine tumors; HR = hazard ratio; HRQoL= health-related quality of life; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression free survival; pNET = pancreatic neuroendocrine tumors.

Note: PFS were analyzed based on the ITT population.

OS and PFS: the trial calculated medians using the Kaplan-Meier method and constructed 95% confidence intervals (CIs) with the Brookmeyer-Crowley methodology. To estimate the HR, the trial used stratified Cox proportional hazards regression models, stratified by randomization strata and tested the difference between groups using the stratified log-rank test.

HRQoL: HRQoL measures combined function and symptom scores to create a summary score. The study calculated descriptive means and 95% CIs; however, the full statistical analysis of HRQoL was not available.

Definition:

* PFS: the time from randomization to radiographic progressive disease, according to RECIST 1.1, as determined retrospectively by blinded independent contral review or death from any cause.

** OS: time from randomization to death from any cause.

*** HRQoL: measured by EORTC QLQ-C30 with higher scores = better HRQoL; reported the mean score and 95% CI; data were plotted in Supplementary Figure 5 of Chan et al. (2025).[10]

Source: Chan et al. (2025)[10] and its supplementary appendix

Harms

Table 5 presents the results for harm outcomes important to this review. Treatment-related AEs and SAEs (judged by the investigator) and all Grade 5 AE (regardless of attribution) were reported. Any grade AEs and AEs of grade 3 to 5 can be found in Table 5 to Table 8 within the supplemental materials document. Key results include the following:

- Compared to the placebo group, patients in the cabozantinib group had higher proportions of any grade treatment-related AEs, SAEs, and WDAEs. Specific AE leading to withdrawal were not reported. The results of planned statistical analyses (i.e., P values) for between-group differences were not reported.[10]

- In the epNET cohort
    - The most common (10% or more) treatment-related grade 3 or 4 adverse events were hypertension (21%), fatigue (13%), and diarrhea (11%).[10] In contrast, the participants in the placebo group experienced these AEs at the following rates: 7% for hypertension, 4% for fatigue, and 3% for diarrhea.
    - Grade 5 events occurred in 9 patients (7%) in the cabozantinib group and 4 patients (6%) in the placebo group.[10]
- In the pNET cohort
    - The most common (10% or more) treatment-related grade 3 or 4 adverse events were hypertension (22%), fatigue (11%), and thromboembolic events (11%).[10] In contrast, the participants in the placebo group experienced these AEs at the following rates: 10% for hypertension, 3% for fatigue, and 0% for diarrhea.
    - No grade 5 AEs were reported.[10]

Table 5: Summary of Key Safety Results

Safety outcomes	epNET cohort		pNET cohort*	
	Cabozantinib, n= 132	Placebo, n=67	Cabozantinib, n=63	Placebo, n=31
Treatment-related AEs, n (%)	130 (98)	55 (82)	62 (98)	26 (84)
Treatment-related SAE (Grade 3 or higher AEs), n (%)	82 (62)	18 (27)	41 (65)	7 (23)
WDAE	34 (31)	9 (15)	10 (20)	0 (0)
Death due to AE	9 (7)	4 (6)	0	0

epNET = extrapancreatic neuroendocrine tumors; NR = not reported; pNET = pancreatic neuroendocrine tumors; SAE = serious adverse event; WDAE = withdrawals due to adverse events. Note: the safety population included all patients who underwent randomization and received at least one dose of intervention or placebo.

* No grade 5 AEs were reported in the pNET cohort.

Discussion

Efficacy

The CABINET trial examined the efficacy of cabozantinib in adults with locally advanced or metastatic epNET or pNET who had received at least one prior therapy.[10] The trial reported relative hazard estimates and medians for assessing cabozantinib's efficacy. The clinical experts consulted by the review team indicated that the observed benefit on PFS was clinically meaningful. Early termination based on interim analysis results could potentially overestimate the magnitude of the treatment effect. The small sample size, especially in the pNET cohort, and the limited ability to appraise for potential missing data for both epNET and pNET cohorts further contribute to uncertainty in effect estimations. While cabozantinib showed improvements in PFS, the evidence was not sufficient to observe an OS difference between the trial groups at the time of analysis. The result may be influenced by the crossover of patients from the placebo group to cabozantinib and the high rate of subsequent anticancer therapies. It is unclear whether further follow-up would change the results.

Compared with other VEGF receptor-targeting tyrosine kinase inhibitors, such as sunitinib, axitinib, and pazopanib, cabozantinib is a multitarget tyrosine kinase inhibitor, including MET and AXL, which may contribute to its efficacy.[14] While sunitinib is approved for pNETs, other inhibitors have shown activity but are not approved in Canada and elsewhere.[15,16]

The generalizability of the study results may be limited by the exclusion of certain patient subpopulations, such as those with poor physical performance scores (ECOG 3 or greater), poorly differentiated neuroendocrine carcinoma, and high-grade neuroendocrine carcinoma without specification of differentiation status. Clinical experts suggest that these patients might benefit from cabozantinib

treatment, but further research is needed to support this. The use of a placebo rather than an active comparator may affect the interpretation of clinical relevance, as the efficacy of therapy for patients with advanced NETs after progression on prior treatments is not well established. No studies were identified that compared cabozantinib with other active comparators (e.g., sunitinib).

Clinician inputs from clinical experts and clinician groups emphasized the need for additional therapies for patients with advanced NETs. Additionally, the views of clinician groups and clinical experts highlight the importance of individualized treatment based on patient preferences and characteristics. Patient group input identified HRQoL, PFS, and OS as important outcomes. The improvement in PFS with cabozantinib supports an advantage for this outcome, but the uncertainty in the OS and HRQoL findings suggests a lack of clarity about whether it meets all of the unmet clinical needs identified by interest-holders. HRQoL appeared to remain stable over time,[10] which may be an important consideration for patients in terms of drug tolerance. However, the high risk of bias in HRQoL data indicates that we need to interpret the findings with caution. The clinical experts consulted for this review noted that, despite the adverse events associated with cabozantinib, the stability and similarity in quality of life between cabozantinib and placebo suggest some benefits for patients in the cabozantinib group.

Although OS was not demonstrated, the clinical experts highlighted that this might be attributed to early trial termination upon meeting the primary endpoint, ethical crossover from the placebo arm to active treatment, and the indolent nature of epNETs and pNETs, which makes demonstrating OS benefit challenging. The clinical experts indicated that similar patterns have been seen in other NET trials, such as NETTER-1, where PFS benefit did not translate into OS benefit.[17] Clinical experts believed that conducting a larger trial with OS as the primary endpoint would not be feasible.

Harms

Cabozantinib treatment in patients with advanced NETs has been associated with an increased incidence of adverse events compared to placebo. Common treatment-related adverse events included hypertension, fatigue, diarrhea, and thromboembolic events.[10] Grade 3 or higher adverse events occurred in 62% or 65% of patients treated with cabozantinib, compared to 27% or 23% of patients receiving placebo in the epNET and pNET cohorts, respectively.[10] Clinical experts suggest that while these safety issues are significant, they are generally manageable in clinical practice through dose modifications and supportive care measures. Patient group input highlights that despite the high incidence of adverse events, patients may consider these harms acceptable if the drug provides significant clinical benefits.

Several limitations may affect the interpretation of safety results.[10] Early termination of the trial based on interim analysis results precluded the ability to assess longer-term adverse events.[10] Using placebo rather than an active comparators may limit understanding of relative safety compared to other active treatments.[10] The absence of long-term safety data and direct comparative data versus relevant active comparators are gaps in the current evidence.

Conclusion

The CABINET trial[10] provides evidence that cabozantinib significantly improves PFS in adults with locally advanced or metastatic epNET or pNET who have progressed after prior therapies. This efficacy aligns with patient expectations for extended disease control. There is some uncertainty in the findings due the interim nature of the analysis, small sample size, and limited ability to appraise for potential missing data. The evidence was insufficient to show a benefit of cabozantinib on OS. Longer follow-up for OS may be informative, however, allowance for crossover from placebo to cabozantinib will challenge the ability to observe a difference between groups. HRQoL was not analyzed statistically and was at risk of bias due to missing outcome data. The safety profile of cabozantinib, characterized by a high incidence of grade 3 or higher adverse events such as hypertension, fatigue, and diarrhea, requires careful management and dose adjustments. The lack of data on specific populations, such as those with poor ECOG performance scores, leads to uncertain generalizability in these populations. We did not identify any studies comparing the efficacy and safety of cabozantinib and other active comparators in advanced or metastatic NETs.

Economic Review

The economic review consisted of a cost comparison for cabozantinib compared with everolimus, sunitinib, CAPTEM and lu-177 DOTATATE for adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy. CAPTEM was considered a comparator only for pancreatic neuroendocrine tumours.

Based on public list prices, cabozantinib is expected to have a per patient cost of $8,436 per 28-days. Everolimus, sunitinib, CAPTEM and lu-177 DOTATATE are expected to have per patient costs of $4,823, $4,650, $813 and $17,500 per 28 days, respectively (Table 10, Appendix 6). Therefore, the incremental costs of cabozantinib per patient per 28-day cycle are $3,613, $3,786, and $7,623 compared to everolimus, eunitinib and CAPTEM, respectively. Compared to lu-177 DOTATATE , cabozantinib is associated with incremental savings of $9,064. As such, the impact of the reimbursement of cabozantinib for the treatment of locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy is contingent on which treatments are displaced. Additional items for consideration are provided in the following bullets:

- According to the clinical review, evidence from the CABINET trial[10] assessing the efficacy and safety of cabozantinib compared with placebo in adults with locally advanced or metastatic epNET or pNET who have progressed after prior therapies suggests that cabozantinib improved PFS and increased the incidence of grade 3 or higher side effects. Results of OS were uncertain due to short follow-up. No evidence was identified regarding the comparative efficacy and safety of cabozantinib versus other active comparators.
- As of April 2025, cabozantinib is only available as a brand name product in Canada. There are 2 generics under review at Health Canada(Table 1).
- No healthcare resource use outcomes were reported in the clinical trial.[10]
- According to the clinical experts consulted for this review, cabozantinib is expected to have similar treatment-related healthcare resource use compared with other treatments available in Canada. They noted that lu-177 DOTATATE is a radioactive therapy that is only administered in a tertiary referral centre with dedicated nuclear medicine and/or radiation oncology and therefore, it is expected that cabozantinib would have lower administration costs when compared with lu-177 DOTATATE.
- Cabozantinib was previously reviewed by CDA-AMC for different indications only. CDA-AMC previously reviewed lu-177 DOTATATE (2022), everolimus (2016) and sunitinib (2012) for patients with NETs with positive recommendations for reimbursement.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on May 20, 2025

Conclusion

The impact of the reimbursement of cabozantinib for the treatment of locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy is uncertain. Based on public list prices, cabozantinib will result in higher drug costs to the health system compared to most comparators (everolimus, sunitinib, and CAPTEM), with the exception of lu-177 DOTATATE, against which cabozantinib will result in lower costs. It is unknown whether there is clinical benefit when comparing cabozantinib versus all relevant comparators.

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