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

Reimbursement Review

Cabozantinib (N/A)

Draft Supplemental Material

Therapeutic area: Neuroendocrine tumours

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.

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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 Appendices

Appendix 1: Characteristics of cabozantinib and comparators

Table 1: Key Characteristics of cabozantinib and comparators

Treatment	Mechanism of action	Related Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
Cabozantinib (tablet)	Tyrosine kinase inhibitor .	No Health Canada indication for NETs	Monotherapy Oral: 60 mg Daily; adjust dosage according to tolerance: 40 mg Daily, 20 mg daily, or discontinue. Note: Cabozantinib tablets and capsules are **NOT** interchangeable.	Hypertension, hand-foot syndrome, diarrhea, proteinuria, fatigue, severe hemorrhage, hepatic toxicity.
Comparators				
Somatostatin analogues, lanreotide or octreotide	These agents exert a dual effect: inhibiting the release of various hormones and exerting cytostatic effects by binding to somatostatin receptors.	Enteropancreatic neuroendocrine tumours; carcinoid syndrome or tumors	Subcutaneous or intramuscular, varies by specific drug	Gastrointestinal, metabolic, and cardiovascular effects, such as gallstones, hyperglycemia, hypothyroidism
Everolimus	mTOR inhibitor	pNET or NET of Gastrointestinal or lung origin	Oral: 60 mg Daily	Infections, kidney failure
Sunitinib	tyrosine kinase inhibitor	pNETs	Oral: 50 mg Daily	Cardiovascular events, hemorrhagic events, kidney failure
Capecitabine plus temozolomide	Capecitabine: inhibits thymidylate synthase; Temozolomide: alkylates/methylates DNA	Glioblastoma multiforme or anaplastic astrocytoma	Oral, dosage varies	Hematological toxicity, gastrointestinal adverse events
Peptide receptor radionuclide therapy (Lutetium-177 dotatate)	Delivers targeted radiation therapy	Somatostatin receptor-positive Gastroenteropancreatic NETs	Intravenous, dosage varies	Kidney damage, bone marrow suppression

[a] Health Canada–approved indication. epNET = extra-pancreatic neuroendocrine tumors; DNA = Deoxyribonucleic acid; NET = neuroendocrine tumors; pNET = pancreatic neuroendocrine.tumors.

Clinical Review Appendices

Appendix 2: Methods of the Clinical Review

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were cabozantinib and neuroendocrine tumours. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 5, 2025. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on July 17, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials.

A focused literature search for indirect treatment comparisons (ITCs) dealing with cabozantinib or neuroendocrine tumours was run in MEDLINE on March 4, 2025. No limits were applied.

Search Strategies

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 5, 2025

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits

- Publication date limit: none

- Language limit: none
- Conference abstracts: excluded

Table 2: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1 (Cabometyx* or Dabatrox* or Exobozan* or Zanterib* or Cometriq* or Cabanib* or Caboxen* or Cabozanix* or Cabotib* or Cabozanib* or Cazanat* or Aptimetyx* or Cabometix* or cabozantinib* or BMS-907351 or BMS907351 or XL-184 or XL184 or 1C39JW444G).ti,ab,kf,ot,hw,rn,nm.

2 Neuroendocrine Tumors/ or exp Carcinoid Tumor/ or Carcinoma, Neuroendocrine/ or exp Islet Cell Tumors/ or Adenoma, Acidophil/ or Adenoma, Basophil/ or Adenoma, Chromophobe/ or Apudoma/ or Carcinoma, Medullary/ or Somatostatinoma/ or Vipoma/ or exp Melanoma/ or exp Neurilemmoma/ or exp Paraganglioma/

3 (neuroendocrine* or neuro-endocrine* or adenoneuroendocrine* or adeno-neuroendocrine* or carcinoid* or gastrinoma* or insulinoma* or glucagonoma* or somatostatinoma* or VIPoma* or argentaffinoma* or ph?eochromocytoma* or paraganglioma* or adenoma* or microadenoma* or micro-adenoma* or macroadenoma* or macro-adenoma* or apudoma* or neurilemmoma* or melanoma* or medullary carcinoma* or NETs or NENs or NECs or PanNET? or Pan-NET? or PanNEN? or Pan-NEN? or PanNEC? or Pan-NEC? or SiNET? or Si-NET? or MiNEN? or SiNEN? or Si-NEN? or pNET or pNETS or p-NET or p-NETs or pNEN? or p-NEN? or epNET? or ep-NET? or epNEN? or ep-NEN? or SBNET? or SB-NET? or SBNEN? or SB-NEN? or GEPNET? or GEP-NET? or GEPNEN? or GEP-NEN? or GENET? or GE-NET? or GENEN? or GE-NEN? or GINET? or GI-NET? or GINEN? or GI-NEN? or LNET? or L-NET? or LCNEC? or GNET? or G-NET? or GNEN? or G-NEN? or GNEC? or G-NEC? or PHNEN? or PH-NEN? or PitNET? or Pit-NET? or aNET or aNETs or a-NETs or SCNC? or SCNEC? or NEPC?).ti,ab,kf.

4 ((thoracic or lung* or bronch* or thymus or thymic or pancrea* or gastro* or gastric or stomach* or islet* or foregut* or fore-gut* or midgut* or mid-gut* or hindgut* or hind-gut* or pituitary or presacral or prostat* or appendiceal or appendix or colorectal or colon or rectal or rectum or intestin* or bowel* or duoden* or ileal or ileum) adj1 (NEN or NET or NEC)).ti,ab,kf.

5 ((islet or islets or alpha cell* or beta cell* or diarrheogenic) adj3 (adenoma? or cancer* or carcinoma? or malignanc* or neoplas* or polypeptidoma* or sarcoma* or tumor* or tumour*)).ti,ab,kf.

6 2 or 3 or 4 or 5

7 1 and 6

8 7 use medall

9 *Cabozantinib/

10 (Cabometyx* or Dabatrox* or Exobozan* or Zanterib* or Cometriq* or Cabanib* or Caboxen* or Cabozanix* or Cabotib* or Cabozanib* or Cazanat* or Aptimetyx* or Cabometix* or cabozantinib* or BMS-907351 or BMS907351 or XL-184 or XL184).ti,ab,kf,dq.

11 9 or 10

12 Neuroendocrine Tumor/ or apudoma/ or exp carcinoid/ or exp gastroenteropancreatic neuroendocrine tumor/ or exp thymic neuroendocrine tumor/ or exp catecholamine-producing tumor/ or neuroendocrine carcinoma/ or mixed adenoneuroendocrine carcinoma/ or neuroendocrine carcinoma of the gallbladder/ or neuroendocrine carcinoma of the prostate/ or small cell carcinoma of the bladder/ or thymic neuroendocrine carcinoma/ or exp paraganglioma/ or exp pineal body tumor/ or hypophysis tumor/ or exp craniopharyngioma/ or pituitary carcinoma/ or pituitary incidentaloma/ or Rathke cleft cyst/ or sella turcica tumor/ or hypophysis adenoma/ or familial isolated pituitary adenoma/ or functioning pituitary adenoma/ or exp nonfunctioning pituitary adenoma/ or pituitary macroadenoma/ or pituitary microadenoma/ or ACTH secreting adenoma/ or gonadotroph adenoma/ or growth hormone secreting adenoma/ or plurihormonal adenoma/ or exp prolactinoma/ or thyrotropin secreting adenoma/ or exp hypothalamus tumor/

13 (neuroendocrine* or neuro-endocrine* or adenoneuroendocrine* or adeno-neuroendocrine* or carcinoid* or gastrinoma* or insulinoma* or glucagonoma* or somatostatinoma* or VIPoma* or argentaffinoma* or ph?eochromocytoma* or paraganglioma* or adenoma* or microadenoma* or micro-adenoma* or macroadenoma* or macro-adenoma* or apudoma* or neurilemmoma* or melanoma* or medullary carcinoma* or NETs or NENs or NECs or PanNET? or Pan-NET? or PanNEN? or Pan-NEN? or PanNEC? or Pan-NEC? or SiNET? or Si-NET? or MiNEN? or SiNEN? or Si-NEN? or pNET or pNETS or p-NET or p-NETs or pNEN? or p-NEN? or epNET? or ep-NET? or epNEN? or ep-NEN? or SBNET? or SB-NET? or SBNEN? or SB-NEN? or GEPNET? or GEP-NET? or GEPNEN? or GEP-NEN? or GENET? or GE-NET? or GENEN? or GE-NEN? or GINET? or GI-NET? or GINEN? or GI-NEN? or LNET? or L-NET? or LCNEC? or GNET? or G-NET? or GNEN? or G-NEN? or GNEC? or G-

NEC? or PHNEN? or PH-NEN? or PitNET? or Pit-NET? or aNET or aNETs or a-NETs or SCNC? or SCNEC? or NEPC?).ti,ab,kf.

14 ((thoracic or lung* or bronch* or thymus or thymic or pancrea* or gastro* or gastric or stomach* or islet* or foregut* or fore-gut* or midgut* or mid-gut* or hindgut* or hind-gut* or pituitary or presacral or prostat* or appendiceal or appendix or colorectal or colon or rectal or rectum or intestin* or bowel* or duoden* or ileal or ileum) adj1 (NEN or NET or NEC)).ti,ab,kf.

15 ((islet or islets or alpha cell* or beta cell* or diarrheogenic) adj3 (adenoma? or cancer* or carcinoma? or malignanc* or neoplas* or polypeptidoma* or sarcoma* or tumor* or tumour*)).ti,ab,kf.

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Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.
[Search -- (Cabometyx* OR Dabatrox* OR Exobozan* OR Zanterib* OR Cometriq* OR Cabanib* OR Caboxen* OR Cabozanix* OR Cabotib* OR Cabozanib* OR Cazanat* OR Aptimetyx* OR Cabometix* OR cabozantinib* OR "BMS-907351" OR BMS907351 OR "XL-184" OR XL184) AND (neuroendocrine* OR "neuro-endocrine" OR adenoneuroendocrine* OR "adeno-neuroendocrine" OR carcinoid* OR gastrinoma* OR insulinoma* OR glucagonoma* OR somatostatinoma* OR VIPoma* OR argentaffinoma* OR pheochromocytoma* OR phaeochromocytoma* OR paraganglioma* OR NETs OR NENs OR NECs)]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
[Search terms -- (Cabometyx* OR Dabatrox* OR Exobozan* OR Zanterib* OR Cometriq* OR Cabanib* OR Caboxen* OR Cabozanix* OR Cabotib* OR Cabozanib* OR Cazanat* OR Aptimetyx* OR Cabometix* OR cabozantinib* OR "BMS-907351" OR BMS907351 OR "XL-184" OR XL184) AND (neuroendocrine* OR "neuro-endocrine" OR adenoneuroendocrine* OR "adeno-neuroendocrine" OR carcinoid* OR gastrinoma* OR insulinoma* OR glucagonoma* OR somatostatinoma* OR VIPoma* OR argentaffinoma* OR pheochromocytoma* OR phaeochromocytoma* OR paraganglioma* OR NETs OR NENs OR NECs)]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.
[Search terms -- Cabometyx, Dabatrox, Exobozan, Zanterib, Cometriq, Cabanib, Caboxen, Cabozanix, Cabotib, Cabozanib, Cazanat, Aptimetyx, Cabometix, cabozantinib, BMS-907351, BMS907351, XL-184, XL184]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- (Cabometyx* OR Dabatrox* OR Exobozan* OR Zanterib* OR Cometriq* OR Cabanib* OR Caboxen* OR Cabozanix* OR Cabotib* OR Cabozanib* OR Cazanat* OR Aptimetyx* OR Cabometix* OR cabozantinib* OR "BMS-907351" OR BMS907351 OR "XL-184" OR XL184) AND (neuroendocrine* OR "neuro-endocrine" OR adenoneuroendocrine* OR "adeno-neuroendocrine" OR carcinoid* OR gastrinoma* OR insulinoma* OR glucagonoma* OR somatostatinoma* OR VIPoma* OR argentaffinoma* OR pheochromocytoma* OR phaeochromocytoma* OR paraganglioma* OR NETs OR NENs OR NECs)]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- Cabometyx, Dabatrox, Exobozan, Zanterib, Cometriq, Cabanib, Caboxen, Cabozanix, Cabotib, Cabozanib, Cazanat, Aptimetyx, Cabometix, cabozantinib, BMS-907351, BMS907351, XL-184, XL184]

Grey Literature

Search dates: February 11-19, 2025

Keywords: Cabozantinib, Cabometyx, Cometriq, neuroendocrine, "neuro endocrine"

Limits: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist. Critical appraisal of the included studies was guided by the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0).[2]

Excluded Studies

Table 2 Excluded Studies

Study	Reason for exclusion
Studies excluded from the systematic review	
Killock D. CABINET presents cabozantinib as a new treatment option for NETs. Nature Reviews Clinical Oncology. 2024;21(11):766. doi:10.1038/s41571-024-00949-0.	Review
Schlumberger M, Elisei R, Muller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28(11):2813-2819. doi:10.1093/annonc/mdx479. PubMed: PM29045520	Wrong population
Daud A, Kluger HM, Kurzrock R, et al. Phase II randomised discontinuation trial of the MET/VEGF receptor inhibitor cabozantinib in metastatic melanoma. Br J Cancer. 2017;116(4):432-440. doi:10.1038/bjc.2016.419. PubMed: PM28103611	Wrong study design
Miles DR, Lacy SA, Wada DR, Milwee S, Yaron Y, Nguyen LT. Assessment of cabozantinib treatment on QT interval in a phase 3 study in medullary thyroid cancer: evaluation of indirect QT effects mediated through treatment-induced changes in serum electrolytes. Cancer Chemother Pharmacol. 2017;80(2):295-306. doi:10.1007/s00280-017-3349-y. PubMed: PM28634649	Wrong population
Krajewska J, Olczyk T, Jarzab B. Cabozantinib for the treatment of progressive metastatic medullary thyroid cancer. Expert Rev Clin Pharmacol. 2016;9(1):69-79. doi:10.1586/17512433.2016.1102052. PubMed: PM26536165	Wrong population
Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639-46. doi:10.1200/jco.2012.48.4659. PubMed: PM24002501	Wrong population
Excluded indirect treatment comparisons	
Walter MA, Nesti C, Spanjol M, et al. Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta-analysis. Cochrane Database Syst Rev. 2021;11:CD013700. doi:10.1002/14651858.CD013700.pub2. PubMed: PM34822169	Wrong intervention
Tsoli M, Alexandraki KI, Spei ME, Kaltsas GA, Daskalakis K. Anti-Tumor Activity and Safety of Multikinase Inhibitors in Advanced and/or Metastatic Thyroid Cancer: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Horm Metab Res. 2020;52(1):25-31. doi:10.1055/a-1023-4214. PubMed: PM31665790	Wrong population

Kaderli RM, Spanjol M, Kollar A, et al. Therapeutic Options for Neuroendocrine Tumors: A Systematic Review and Network Meta-analysis. JAMA Oncol. 2019;5(4):480-489. doi:10.1001/jamaoncol.2018.6720. PubMed: PM30763436	Wrong intervention
Shi X, Dong X, Young S, et al. The impact of angiogenesis inhibitors on survival of patients with small cell lung cancer. Cancer Med. 2019;8(13):5930-5938. doi:10.1002/cam4.2462. PubMed: PM31433125	Wrong population
Tappenden P, Carroll C, Hamilton J, et al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model. Health Technology Assessment (Winchester, England). 2019;23(8):1-144. doi:10.3310/hta23080. PubMed: PM30821231	Wrong population
Strosberg JR, Al-Toubah T, Cives M. Evaluating Risks and Benefits of Evolving Systemic Treatments of Neuroendocrine Tumors. JAMA Oncol. 2019;5(4):489-490. doi:10.1001/jamaoncol.2018.6694. PubMed: PM30763444	Wrong intervention

Appendix 3: Methods of the Studies Included in the Systematic Review

Characteristics of the Included Study

Inclusion and Exclusion Criteria

Table 3: Details of Study Included in the Systematic Review

Included study	Inclusion criteria	Exclusion Criteria
CABINET trial by Chan et al. (2025)[3]	• Age: Patients 18 years or older. • Diagnosis: Histologically confirmed, locally advanced or metastatic well- or moderately differentiated epNET or pNET. • Tumor grade: WHO tumor grades 1 to 3. • Tumor Site: Histological documentation of neuroendocrine tumor of pancreatic, gastrointestinal, lung, thymus, other, or unknown primary site; gastrointestinal, lung, thymus, other, and unknown primary NETs will enroll in the carcinoid tumor cohort of the study • Functional (i.e., associated with symptoms or clinical syndrome related to hormone secretion by tumor) or nonfunctional tumors are allowed. • Disease Progression: Progressive disease according to RECIST 1.1 within 12 months before enrollment. • Performance status: ECOG performance-status score of 0 to 2. • Previous therapy: Disease progression or unacceptable side effects after at least one FDA-approved line of therapy, depending on the primary tumour site, including somatostatin analogs, Lu-177 dotatate, everolimus, or sunitinib.	• Diagnosis: Poorly differentiated neuroendocrine carcinoma or high-grade neuroendocrine carcinoma (unspecified differentiation status) • Concurrent Conditions: Any condition that hinders the patient's ability to comply with the study protocol, for example: ○ class III or IV congestive heart failure within 6 months of registration ○ clinically significant cardiac arrhythmia within 6 months of registration ○ unstable angina or myocardial infarction within 6 months of registration ○ thromboembolic events within 6 months of registration ○ known history of congenital long QT syndrome ○ uncontrolled hypertension within 14 days of registration ○ clinically significant gastrointestinal bleeding within 6 months of registration ○ clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of registration

ECOG = Eastern Cooperative Oncology Group; epNET = extra-pancreatic neuroendocrine tumors; FDA= Food and Drug Administration; NET = neuroendocrine tumors; pNET = pancreatic neuroendocrine tumors; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; WHO = World Health Organization.

Source: Chan et al. (2025);[3] ClinicalTrials.gov (NCT03375320)[4]

Interventions and Comparators[3]

In the cabozantinib group, patients receive cabozantinib S-malate orally once daily on days 1-28 of each cycle. Cycles repeat every 28 days unless there is disease progression or unacceptable toxicity. Patients also undergo blood and urine sample collection, as well as CT, MRI, and/or x-ray imaging during screening and throughout the study.

In the placebo group, patients receive a placebo orally once daily on days 1-28 of each cycle. Cycles repeat every 28 days unless there is disease progression or unacceptable toxicity. Patients also undergo blood and urine sample collection, as well as CT, MRI, and/or x-ray imaging during screening and throughout the study.

Appendix 4: Results of the Study Included in the Systematic Review

Characteristics of Patients in the Included Study[3]

Table 4: Summary of Additional Baseline Characteristics From Study Included in the Systematic Review

Characteristics	epNET cohort (n= 203)		pNET cohort (n= 95)	
	Cabozantinib, n=134	Placebo, n=69	Cabozantinib, n=64	Placebo, n=31
Time from diagnosis to randomization, months, median (range)	65 (10-489)	76 (13-340)	71 (18-213)	73 (18-230)
Sex , n (%)				
Female	74 (55)	31 (45)	27 (42)	13 (42)
Male	60 (44)	38 (55)	37 (58)	18 (58)
Race, n (%)				
American Indian/Alaskan Native	-	-	1 (2)	0 (0)
Asian	3 (2)	1 (1)	4 (6)	0 (0)
Black or African American	9 (7)	7 (10)	3 (5)	3 (10)
More than one race reported	-	-	1 (2)	0 (0)
Native Hawaiian/Pacific Islander	-	-	1 (2)	0 (0)
White	115 (86)	55 (80)	54 (84)	25 (81)
Unknown	5 (4)	2 (3)	0 (0)	1 (3)
Not reported	2 (1)	4 (6)	0 (0)	2 (6)
Concurrent SSA, n (%)	92 (69)	48 (70)	35 (55)	17 (55)
Number of prior systemic therapies, median (range)	2 (1-6)	2 (1-6)	3 (1-9)	2 (1-7)
Prior locoregional therapy, n (%)	45 (34)	29 (42)	36 (56)	10 (32)
Prior surgery for metastatic site, n (%)	43 (32)	17 (25)	18 (29)	7 (24)
Prior radiation for metastatic site, n (%)	30 (22)	12 (17)	6 (10)	4 (14)

epNET = extra-pancreatic neuroendocrine tumors; pNET = pancreatic neuroendocrine tumors; SSA = somatostatin analogue.

Source: Chan et al. (2025);[3]

Detailed efficacy outcomes

Detailed Harm Results

Table 5: Summary of Additional Adverse Events (Grade 3-5) From Study Included in the Systematic Review for epNET cohort

Safety outcomes, n (%)	ep-NET cohort	
	Cabozantinib, n= 132	Placebo, n=67
Fatigue	17 (13)	5 (7)
Diarrhea	14 (11)	3 (4)
AST increase	4 (3)	0
ALT increase	1 (1)	0
Hypertension	28 (21)	2 (3)
Thrombocytopenia	1 (1)	1 (1)
Nausea	2 (2)	0
Oral mucositis	5 (4)	0
Palmar–plantar erythrodysesthesia	4 (3)	0
Anorexia	2 (2)	0
Dysgeusia	0	0
Neutropenia	4 (3)	0
Leukopenia	4 (3)	0
Anemia	2 (2)	0
Lymphopenia	5 (4)	0
Hypothyroidism	0	0
Maculopapular rash	0	0
Weight loss	3 (2)	0

ALT= alanine aminotransferase; AST = aspartate aminotransferase; epNET = extrapancreatic neuroendocrine tumors.
Source: Chan et al. (2025)[3]

Table 6: Summary of Additional Adverse Events (Grade 3 or 4) From Study Included in the Systematic Review for pNET cohort

Safety outcomes, n (%)	pNET cohort	
	Cabozantinib, n=63	Placebo, n=31
Fatigue	7 (11)	1 (3)
Diarrhea	4 (6)	0
AST increase	1 (2)	0
ALT increase	1 (2)	0
Hypertension	14 (22)	3 (10)
Thrombocytopenia	0	0
Nausea	5 (8)	1 (3)
Oral mucositis	5 (8)	0
Palmar–plantar erythrodysesthesia	6 (10)	0
Anorexia	1 (2)	0
Dysgeusia	0	0
Neutropenia	1 (2)	0
Alkaline phosphatase increase	0	0
Vomiting	4 (6)	0
Hypophosphatemia	0	0
Thromboembolic event	7 (11)	0

ALT= alanine aminotransferase; AST = aspartate aminotransferase; pNET = pancreatic neuroendocrine tumour. Source: Chan et al. (2025)[3]

Table 7: Summary of Additional Adverse Events (any Grade) From Study Included in the Systematic Review for epNET cohort

Safety outcomes, n (%)	ep-NET cohort	
	Cabozantinib, n= 132	Placebo, n=67
Fatigue	82 (62)	28 (42)
Diarrhea	74 (56)	20 (30)
AST increase	86 (65)	12 (18)
ALT increase	77 (58)	9 (13)
Hypertension	70 (53)	13 (19)
Thrombocytopenia	62 (47)	5 (7)
Nausea	46 (35)	10 (15)
Oral mucositis	48 (36)	6 (9)
Palmar–plantar erythrodysesthesia	48 (36)	5 (7)
Anorexia	40 (30)	6 (9)
Dysgeusia	45 (34)	1 (1)
Neutropenia	40 (30)	2 (3)
Leukopenia	46 (35)	2 (3)
Anemia	28 (21)	8 (12)
Lymphopenia	31 (23)	6 (9)
Hypothyroidism	36 (27)	1 (1)
Maculopapular rash	30 (23)	2 (3)
Weight loss	28 (21)	2 (3)

ALT= alanine aminotransferase; AST = aspartate aminotransferase; epNET = extrapancreatic neuroendocrine tumors.
Source: Chan et al. (2025)[3]

Table 8: Summary of Additional Adverse Events (any Grade) From Study Included in the Systematic Review for pNET cohort

Safety outcomes, n (%)	pNET cohort*	
	Cabozantinib, n=63	Placebo, n=31
Fatigue	47 (75)	10 (32)
Diarrhea	37 (59)	4 (13)
AST increase	40 (63)	9 (29)
ALT increase	39 (62)	9 (29)
Hypertension	36 (57)	7 (23)
Thrombocytopenia	21 (33)	3 (10)
Nausea	24 (38)	7 (23)
Oral mucositis	30 (48)	1 (3)
Palmar–plantar erythrodysesthesia	28 (44)	4 (13)
Anorexia	13 (21)	3 (10)
Dysgeusia	19 (30)	3 (10)
Neutropenia	17 (27)	2 (6)
Alkaline phosphatase increase	13 (21)	3 (10)
Vomiting	13 (21)	3 (10)
Hypophosphatemia	13 (21)	2 (6)
Thromboembolic event	11 (17)	0

ALT= alanine aminotransferase; AST = aspartate aminotransferase; pNET = pancreatic neuroendocrine tumor.
* No grade 5 AEs were reported in the pNET cohort.
Source: Chan et al. (2025)[3]

Appendix 5: Critical Appraisal of Included Publication

Table 9: Risk of bias Assessment of Clinical Study Using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)[2]

Domain 1: Risk of bias arising from randomization process		
1.1 Was the allocation sequence random?	Patients were randomized using a stratified permuted block randomization separately in each cohort.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Method allocation concealment could not be found in the study protocol, published article, clinical trial registry, or in the supplementary appendix of the publication. Use of a web-based system mentioned in the protocol suggests that the allocation is likely to be concealed but it cannot be determined with certainty.	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant imbalances in patient baseline characteristics were reported except for a higher proportion of patients with unknown primary tumour sites in the cabozantinib group than in the control group for epNET cohort.	PY
Risk-of-bias judgement	The allocation sequence was likely adequately concealed and there were few apparent differences in characteristics of the patients at baseline in both intervention groups.	Low risk of bias
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	As this study was double-blinded, participants were unaware of the intervention during the trial until disease progression.	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	The trial was described as 'double-blind' but it is not fully clear who was blinded. Whether the physicians who delivered the interventions were aware of the participants' assigned intervention during the trial was not clearly reported but some information in the publication suggest that physicians were likely unaware of the intervention	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	There were no apparent deviations from the intended interventions. Pre-medication and patient disposition were clearly described in the protocol or publications. However, the protocol did not provide details on concomitant treatments, such as how many participants received subsequent treatment before progression, which may introduce bias. Considering the blinding and patient disposition data, the possibility of bias is likely small. Reasons for treatment discontinuation were primarily progression and AEs.	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All prespecified outcomes were analyzed using the intention-to-treat (ITT) population, which is appropriate.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Risk-of-bias judgement	Patients were unaware of the assigned intervention. There is less clarity about whether physicians might be aware of the assigned intervention during the trial, though some information suggests that they likely were. There were no apparent deviations from the intended intervention.	Low risk of bias
Domain 3: Risk of bias due to missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	For PFS, OS, and AEs, the censoring reasons were not provided, making it unclear how many patients might have been censored due to loss to follow-up. Based on the provided disposition, this number appears likely to be low. For HRQoL, the number of patients contributing data decreases substantially over time. The analysis of complete cases assumes that missingness is completely at random, which is not a reasonable assumption given the likely reasons for missingness (e.g., death).	PY for PFS, OS, and AEs; N for HRQoL
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA for PFS, OS, and AEs; No for HRQoL because no sensitivity analyses were provided making different reasonable assumptions about the missing data.	NA for PFS, OS, and AEs; PN for HRQoL
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA for PFS, OS, and AEs; probably yes for HRQoL	NA; PY for HRQoL
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA for PFS, OS, and AEs; probably yes for HRQoL	NA; PY for HRQoL
Risk-of-bias judgement	All randomized patients were included in the efficacy (ITT population) for PFS. Nearly all patients were included for OS and safety outcomes.	Unclear risk of bias for PFS, OS, and AEs; high risk of bias for HRQoL
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	The methods of measuring the outcomes were appropriate and clearly described in the trial protocol and publication.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Methods of outcome measurement and thresholds were similar between intervention groups.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	The outcomes were assessed by the investigators and an independent central review. The patient-reported outcomes for AEs and HRQoL may be influenced by crossover to open label cabozantinib.	PN for OS and PFS; PY for safety and HRQoL outcomes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA for OS and PFS; T The unblinding of cabozantinib post-progression may influence the outcome assessment for safety	NA for OS and PFS; PY for safety

	outcomes (though patients would no longer be receiving cabozantinib or placebo at this time) and HRQoL measures.	outcomes and HRQoL
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA; yes for safety outcomes and HRQoL.	NA for OS and PFS; PY for safety outcomes and HRQoL
Risk-of-bias judgement	The methods of measuring the outcomes were appropriate. The measurements or ascertainment of the outcomes did not differ between intervention groups. The assessment of the safety outcomes could have been influenced by knowledge of the intervention received due to unblinding post-progression.	Some concerns for safety outcomes and HRQoL
Domain 5: Risk of bias in selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Data that produced the results in the published report were analyzed in accordance with a pre-specified analysis plan reported in detail in the trial protocol.	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Efficacy outcomes such as PFS and OS were assessed following their pre-defined analyses, and interim analyses were performed as described in the protocol.	N
5.3 ... multiple eligible analyses of the data?	The protocol was generally followed.	N
Risk-of-bias judgement	The data were analyzed in accordance with a pre-specified plan. The results being assessed were unlikely to have been selected. However, HRQoL analyses have not yet been published, despite being mentioned in the protocol. Additionally, the statistical tests for safety outcomes were not reported.	Low risk of bias for PFS and OS; some concerns for safety outcomes and HRQoL.

N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Economic Review Appendices

Appendix 6: Cost Comparison Table

The comparators presented in Table 10 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the CABINET trial and validated by clinical experts. Pricing for comparator products was based on publicly available list prices, except for lu-177 DOTATATE, which was based on a previous CDA-AMC review.[5]

The recommended dose of cabozantinib is 60 mg once daily (Table 1). At $301.29 per tablet, the treatment acquisition cost of cabozantinib is $301.29 daily, or $8,436 per patient per 28-day course. 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-day cycle, respectively (Table 1). Therefore, the incremental costs of cabozantinib per patient per 28-day cycle are $3,613, $3,786, and $7,623 compared to everolimus, sunitinib and CAPTEM, respectively. Compared to lu-177 DOTATATE, cabozantinib is associated with incremental savings of $9,064. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 10.

Table 10: CDA-AMC Cost Comparison Table for Locally Advanced or Metastatic Extra-Pancreatic or Pancreatic Neuroendocrine Tumours

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	28-day cost ($)
Cabozantinib	20 mg 40 mg 60 mg	Tablet	301.2944[a]	60 mg once daily[b]	301.29	8,436
Kinase inhibitors						
Everolimus	2.5 mg 5 mg 7.5 mg 10 mg	Tablet	172.2559	10 mg daily[b]	172.26	4,823
Sunitinib	12.5 mg 25 mg 50 mg	Capsule	55.3553 110.7100 221.4208	37.5 mg daily[b]	166.07	4,650
CAPTEM						
Capecitabine	150 mg 500 mg	Tablet	0.4575 1.5250	750 mg/m^2 twice daily on Days 1 to 14 every 4 weeks[b]	3.97	111
Temozolomide	5 mg 20 mg 100 mg 140 mg 250 mg	Capsule	1.95 7.8 39.0015 54.6025 97.5010	200 mg/m^2 daily on Days 10 to 14 every 4 weeks[b]	25.07	702
CAPTEM regimen cost per 28 days					29.04	813
Peptide receptor radionuclide therapy (PRRT)						
Lu-177 DOTATATE	370 MBq/mL or 10 mCi/mL (7.4 GBq)	200 mCi vial for IV infusion	35,000.0000[c]	7.4 GBq (200 mCi) IV infusion	625.00	17,500

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	28-day cost ($)
				every 8 weeks for a total of 4 doses[c]		

Note: All prices are from the Ontario Drug Benefit Formulary (accessed April 2025), unless otherwise indicated, and do not include dispensing fees. Costs assume a body weight of 80 kg or a body surface area of 1.8 m^2 and include wastage of unused medication in vials

[a] Ontario Exceptional Access Program (accessed April 2025)[6]

b Cancer Care Ontario Formulary: Regimens database[7]

c CADTH Review Lutathera[5]

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