Canadian Journal of Health Technologies

CADTH

November 2022 Volume 2 Issue 11

CADTH Reimbursement Recommendation

Cabozantinib (Cabometyx)

Indication: For the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible

Sponsor: Ipsen Biopharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Cabometyx?

CADTH recommends that Cabometyx should be reimbursed by public drug plans for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Cabometyx should only be covered to treat patients who did not respond to prior radioactive iodine (RAI) therapy or are not eligible for RAI, those previously treated with 1 to 2 tyrosine kinase inhibitors (TKIs), and those who have good performance status (i.e., they are in relatively good health).

What Are the Conditions for Reimbursement?

Cabometyx should only be reimbursed if it is prescribed by specialists with experience in the management of thyroid cancer and the cost of Cabometyx is reduced.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that patients with DTC treated with Cabometyx experienced benefits in survival without progression of disease. Patients in this trial had side effects that clinical experts considered manageable.

Cabometyx potentially meets important needs since there are currently no funded options available for patients with DTC who have failed to response to RAI and treatment with previous drugs.

Based on CADTH's assessment of the health economic evidence, Cabometyx does not represent good value to the health care system at the public list price. A price reduction is therefore required.

Additional Information

What Is DTC?

Thyroid cancer is cancer that initiates in the thyroid gland. When these cancer cells resemble healthy cells to some degree it is called a differentiated cancer (or carcinoma). People with thyroid cancer whose cancer cells have spread to other parts of the body, such as the lung or bones, likely have advanced or metastatic cancer. In Canada, there are 2 to 3 new cases of DTC per 10,000 people every year (or about 8,600 new cases in total). About a third of these patients will have recurrence of the disease despite treatment, which limits survival and the overall prognosis.

Unmet Needs in DTC

Patients in Canada with advanced or metastatic DTC who do not respond to initial treatment have few treatment options available and not all patients respond to these treatments.

How Much Does Cabometyx Cost?

Treatment with Cabometyx is expected to cost approximately $8,436.24 per patient for a 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that cabozantinib be reimbursed for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory (RAI-R) or ineligible only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase III, randomized, double-blind, placebo-controlled trial (COSMIC-311) demonstrated that treatment with cabozantinib resulted in added progression-free survival (PFS) benefit for patients with advanced or metastatic DTC previously treated with a VEGFR tyrosine kinase inhibitor (TKI) and who are RAI-R. As of the most recent data cutoff date (February 8, 2021), median PFS was 11.1 months (96% confidence interval [CI], 7.4 to 13.8 months) in the cabozantinib group compared to 1.9 months (96% CI, 1.8 to 3.8 months) in the placebo group (P value < 0.0001). Clinical experts consulted by CADTH considered these PFS results to be meaningful for patients and clinicians. In addition, cabozantinib treatment was associated with serious but manageable adverse events (AEs). Overall, pERC recognized that cabozantinib addresses an unmet therapeutic need as there are currently no funded therapies available for patients with RAI-R DTC who have progressed on lenvatinib.

Using the sponsor submitted price for cabozantinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for cabozantinib plus best supportive care (BSC) was $664,742 per quality-adjusted life-year (QALY) compared with BSC alone. At this ICER, cabozantinib is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients with locally advanced or metastatic DTC that have progressed following prior VEGFR-targeted therapy and who are RAI-R or ineligible. A price reduction is required for cabozantinib to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cabozantinib should be reimbursed in patients with DTC who meet all of the following criteria: 1.1. Refractory to prior RAI therapy or not eligible for RAI. 1.2. Previously treated with 1 to 2 prior VEGFR-targeting TKIs. 1.3. Have good performance status.	Patients enrolled in the COSMIC-311 trial must have been previously treated with or deemed ineligible for treatment with RAI, had an ECOG performance status of 0 or 1, and previously treated with 1 to 2 VEGFR-targeting TKIs.	—

Reimbursement condition	Reason	Implementation guidance
Renewal		
2. Cabozantinib should be renewed for patients who exhibit a response to treatment and for whom treatment is tolerable. 2.1. Response should be measured using clinical assessment, biochemical markers, and radiological imaging. 2.2. Patients should be assessed for treatment response every 3 to 4 months or as per physician discretion.	Clinical experts indicated that treatment with cabozantinib would be continued for patients who exhibit a response and tolerate treatment.	When treatment is first started, patients should be assessed every 2 to 3 weeks to monitor for adverse effects and to modify drug dosing, if necessary.
Discontinuation		
3. Cabozantinib should be discontinued if patients experience disease progression or unacceptable toxicity.	Clinical experts indicated that the recommended duration of therapy with cabozantinib in the product monograph is until disease progression or unacceptable toxicity.	—
Prescribing		
4. Patients should be under the care of an oncologist or endocrinologist with expertise in the management of thyroid cancer.	To ensure that cabozantinib is prescribed only for appropriate patients and adverse effects are managed appropriately.	—
Pricing		
5. A reduction in price.	The ICER for cabozantinib + BSC is $664,742 per QALY when compared with BSC. A price reduction of at least 95% would be required for cabozantinib to be able to achieve an ICER of $50,000 per QALY compared to BSC.	—

BSC = best supportive care; DTC = differentiated thyroid carcinoma; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RAI = radioactive iodine; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Discussion Points

- Clinicians expressed a need for effective treatments that improve PFS, overall survival (OS), and health-related quality of life (HRQoL), control symptoms, and have fewer treatment-related harmful adverse effects. pERC discussed that there is an important unmet need

for patients with RAI-R DTC following prior VEGFR-targeted therapy. pERC concluded that cabozantinib likely met some of these needs, such as the need for improved PFS. At the first interim analysis, the COSMIC-311 trial met its end point for PFS, at which point median PFS was not reached (96% CI, 5.7 months to not estimable [NE]) in the cabozantinib group and 1.9 months (96% CI, 1.8 to 3.6 months) in the placebo group (P value < 0.0001). Results from the most recent interim analysis were consistent in showing an improvement in PFS with cabozantinib compared to placebo. OS data were immature and not controlled for multiple comparisons. There is uncertainty regarding the effect of cabozantinib on HRQoL because this outcome was not controlled for multiple comparisons.

- pERC noted that there is a small number of patients with RAI-R DTC in Canada, but a phase III, randomized, double-blind, placebo-controlled trial was feasible. This well-conducted phase III trial demonstrated that cabozantinib resulted in PFS benefit compared to placebo for patients with RAI-R DTC previously treated with a VEGFR TKI.
- There is no evidence on the comparative efficacy or harms of cabozantinib relative to targeted treatments recommended for reimbursement by pERC for the small proportion of patients with DTC that have RET fusions or neurotrophic tyrosine receptor kinase (NTRK) fusions, such as selpercatinib or larotrectinib. pERC noted that these treatments, if funded, would be available only to the minority of patients with the respective targetable fusions. pERC noted that patients with DTC who do not have targetable mutations could be eligible for treatment with cabozantinib.
- pERC discussed that the harms observed in the COSMIC-311 trial were consistent with the known safety profile of cabozantinib and that the adverse effects are serious but anticipated to be clinically manageable. pERC noted that the proportion of patients in the cabozantinib group of the COSMIC-311 trial that discontinued treatment due to an AE was low.

Background

Thyroid cancer is considered to be the most common endocrine malignancy. In 2020, the incidence of thyroid cancer in Canada was estimated to be 23 per 100,000 patients, or about 8,600 new cases. Thyroid cancers arising from thyroid follicular cells include the differentiated thyroid cancer (DTC, which groups papillary thyroid cancer [PTC], follicular thyroid cancer [FTC], and Hurthle cell cancer), poorly differentiated thyroid cancer, and anaplastic thyroid cancer. Among all types of thyroid cancer, DTC is the most common, accounting for more than 95% of cases. In the Canadian population, this will represent approximately 2.7 cases per 10,000 per year.

Thyroid tumours that are localized and well-differentiated usually are curable with total thyroidectomy or lobectomy, followed by postoperative treatment with radioactive iodine (RAI) therapy – for patients at high risk of persistent disease or disease recurrence after total thyroidectomy. Up to 30% of patients with DTC may have recurrence of disease and 60% of these recurrences occur within the first decade after initial therapy. In patients with primary or secondary radioiodine-refractory thyroid carcinoma, the prognosis becomes significantly poorer. Patients with distant metastases have an estimated median survival time of about 2.5 to 3.5 years. The overall mortality rates 5 and 10 years after diagnosis of distant metastases are 65% and 75%, respectively. Early diagnosis and early appropriate surgical treatment are considered to positively affect the prognosis of these patients. In Canada, 2 VEGFR-targeted

TKIs, lenvatinib and sorafenib, are approved for progressive metastatic RAI-resistant cases, but only lenvatinib is currently reimbursed by public drug plans.

Cabozantinib has been approved by Health Canada for the treatment of adult patients with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-refractory or ineligible. Cabozantinib is a multi-targeted TKIs; it is available as oral tablets of 20 mg, 40 mg, and 60 mg. The recommended dosage in the product monograph is 60 mg administered orally once daily without food.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 randomized double-blind, placebo-controlled, clinical trial in patients with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy (COSMIC-311).
- Patients' perspectives gathered by 2 patient groups, the Canadian Cancer Society (CCS) and the Thyroid Cancer Canada organization.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Two clinical specialists with expertise in diagnosing and treating patients with thyroid cancer.
- Input from The Medical Advisory Panel of Thyroid Cancer Canada (TCC) with administrative support provided by the CCS.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups submitted 1 joint input for this review. Canadian Cancer Society (CCS) is the only national charity that supports all Canadians living with all cancers across the country through research, advocacy, and compassionate support activities. Thyroid Cancer Canada (TCC) is a national organization of thyroid cancer survivors dedicated to providing emotional support and information to those affected by the disease. The submission was based on results from a survey distributed by the 2 groups. Two patients responded to the survey, of which 1 had experience with cabozantinib. The patient groups noted that this type of thyroid cancer is rare.

The 2 patients said their ability to work, travel, exercise, conduct household chores, fulfill family obligations, and maintain positive mental health were impacted to a moderate degree by symptoms associated with DTC. Also, both patients indicated there are financial barriers related to treatment (e.g., loss of income, transportation costs). No specific details with respect to outcomes that are important to patients was provided in the input. Of note, patients reported experiencing adverse effects from their treatments such as nausea, vomiting, diarrhea, and fatigue.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Clinical experts consulted by CADTH agreed that RAI-R DTC is a rare disease causing about 200 deaths per year in Canada. The clinical experts indicated that, as with most rare diseases, this raises issues about physician awareness and systemic barriers to access to therapy for patients. Although most patients respond to lenvatinib, all patients will eventually experience disease progression due to acquired drug resistance, per the clinical experts. The clinical experts reported that currently there are no funded and reliably effective treatments for these patients. The clinical experts indicated that treatment goals should be improving OS, PFS, and HRQoL by controlling symptoms, minimizing adverse effects of treatments, and increasing work-life productivity. There is an unmet need, on which both clinical experts agreed, that better treatments must be available for patients who do not respond or progress after first-line therapy, and for those patients who have to discontinue TKI treatment due to side effects or multi-kinase inhibitor resistance. The clinical experts noted that the ideal treatment should also have fewer harmful effects.

Clinical experts agreed that cabozantinib would provide a second-line treatment option for patients progressing despite lenvatinib therapy. Experts also agreed that cabozantinib should not be used as first-line treatment but could be an alternative for patients who are intolerant of lenvatinib. As per the clinical experts, cabozantinib treatment can be associated with significant AEs, so the main criteria for the timing and dosing of treatment would be based on clinical judgment considering patient factors such as tumour burden, age, comorbidities, and performance status. To monitor response, the clinical experts noted that patients should have baseline assessment and imaging and be assessed every 2 to 3 weeks to monitor for adverse effects and to modify drug dosing if necessary. Improved symptoms and a drop in serum thyroglobulin would be favourable signs of response early in treatment, per the clinical experts. The clinical experts indicated that in most patients, cabozantinib would be continued until there is unequivocal evidence of disease progression despite treatment or toxicity. The clinical experts suggested that patients should be under the care of a medical oncologist or endocrinologist experienced in TKI therapy for thyroid cancers. The clinical experts noted that, as RAI-R DTC is a rare condition; currently there is a small community of prescribers in Canada treating this disease. The clinical experts noted that indications for cabozantinib are growing, and a growing number of medical oncologists are becoming familiar with it.

Clinician Group Input

The Medical Advisory Panel of TCC with administrative support provided by the Canadian Cancer Society provided input for this review. A total of 7 physicians (5 from Ontario, 1 from British Columbia, 1 from Alberta) were included and responded to the call for input.

In agreement with the clinical experts consulted by CADTH, the clinician group mentioned the lack of approved/funded options for patients with DTC who are radioactive iodine-refractory (or ineligible) and progress after VEGFR-targeted therapies. The clinician group believes that cabozantinib is expected to fill an urgent unmet need for patients who progress on prior therapy, since no other therapies are funded beyond lenvatinib as first-line treatment in Canada. The clinician group considers that the inclusion criteria for the COSMIC-311 trial define the patient population best suited for cabozantinib treatment. In addition to the criteria listed in the COSMIC-311 trial, patients with progressing non-measurable disease, such as bone metastases, should not be excluded in the real-world clinical setting; this was also in alignment with the input from the clinical experts. To assess response to treatment, clinical

assessment, tumour markers, and radiological imaging, such as CT or MRI scans should generally be done every 3 to 4 months.

The group emphasized that RAI-R DTC is a rare disease with significant unmet need and cabozantinib should be reviewed in this regard.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

pERC agreed with the responses provided by the clinical experts consulted by CADTH to each of the questions from the drug programs in Table 2.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Placebo was chosen as the comparator in the COSMIC-311 study due to the lack of available treatments in this population.	Comment from the drug programs to inform pERC deliberations.
There are no standard comparators funded in Canada at this time.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Should patients who experience adverse effects with lenvatinib or sorafenib without progression be eligible for treatment with cabozantinib?	For most scenarios, the adverse effects of lenvatinib can be managed with dose modifications or use of adjunctive medications (e.g., for hypertension). There may be very uncommon scenarios (e.g., true drug allergy, or hypertension requiring multiple antihypertensive drugs) where cabozantinib should be considered as an alternative.
Considerations for renewal of therapy	
Patients in the COSMIC-311 trial were assessed every 8 weeks for 12 months, then every 12 weeks until clinical benefit was no longer experienced or intolerable toxicity. In clinical practice what is the most appropriate frequency to determine treatment response?	Clinical assessment, tumour markers, and radiological imaging CT or MRI scans should be done every 3 to 4 months as assessment measures of treatment response.
Considerations for discontinuation of therapy	
In the trial, patients were able to continue cabozantinib as long as there was continued clinical benefit in the opinion of the investigator. What are the discontinuation criteria for cabozantinib?	For some patients it may be impossible to titrate cabozantinib to a tolerable dose, and the drug may be discontinued due to adverse effects. In most patients, cabozantinib would be continued until there is unequivocal evidence of disease progression despite treatment.
Considerations for prescribing of therapy	
The recommended dose is 60 mg once daily without food. Dose interruptions are recommended for CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Upon resolution the dose can be reduced to 40 mg daily then to 20 mg daily.	Comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
The drug plans asked pERC whether patients with brain metastases or bone metastases would be eligible for treatment with cabozantinib. Furthermore, the drug plans asked pERC whether it is safe to administer cabozantinib in patients who recently received radiation therapy for bone or brain metastases, or if there is a specific time frame to avoid.	pERC agreed that patients with brain metastases or bone metastases could be treated with cabozantinib according to physician judgment. pERC noted that patients were ineligible for the COSMIC-311 trial if they had received radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks. Patients with brain metastases were eligible for the COSMIC-311 trial if they were adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks. The clinical experts noted that while receiving drug therapy for DTC, a patient may show progression in 1 or 2 areas without other signs of progressive disease and be offered stereotactic body radiation therapy to these areas plus continued drug therapy.
Generalizability	
Can the trial results be generalized to patients with ECOG > 2?	Clinical experts considered that ECOG PS above 2 would be inadvisable due to the risk of serious adverse events.
Care provision issues	
Cabozantinib has potential for drug-drug, drug-food, and drug-herb interactions, requiring assessment and/or intervention.	Understanding of this potential is part of the need for treatment to be administered by practitioners with experience in managing RAI-R DTC. Pharmacists will be able to help manage the drug interactions with cabozantinib.

CTCAE = Common Terminology Criteria for Adverse Events; DTC = differentiated thyroid carcinoma; ECOG = Eastern Cooperative Oncology Group; pERC = pCODR Expert Review Committee; RAI-R = radioactive iodine-refractory.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III clinical study was included in the systematic review. The COSMIC-311 is a randomized, double-blind, placebo-controlled trial, conducted in several centres across Europe, Asia, Latin America, US, and Canada to evaluate the efficacy and safety of cabozantinib 60 mg once daily versus placebo. The randomization was stratified by age (< 65 or ≥ 65 years) and previous use of lenvatinib. The population included patients with advanced or metastatic DTC previously treated with a VEFGR-TKI and who are RAI-resistant. The key end points of objective response rate (ORR), PFS, OS, duration of response, and HRQoL were assessed in an initial cutoff date (August 19, 2020). There was a total of 187 randomized patients (the intention to treat [ITT] and safety population), from which the first 100 randomized patients were obtained and assessed as a specific ITT population for the primary end points of ORR and PFS (i.e., the OITT population). A second cutoff date (February 8, 2021) with a total of 187 patients in the primary analysis subset and 258 patients in the full ITT population, provided longer follow-up assessments, including safety. Crossover to cabozantinib was permitted throughout the study for eligible patients who experienced radiographic disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent radiology committee. Patients in the COSMIC-311 had advanced or metastatic DTC with Eastern Cooperative Oncology Group (ECOG)

performance status (PS) of 0 or 1, with a slight predominance of female patients, and an average age of 65 years.

Efficacy Results

For OS at the data cutoff date of August 19, 2020, with a median follow-up time of 6.24 months, the median OS was not reached (95% CI, not estimable [NE] to NE) in either treatment group. The log-rank test for differences in the Kaplan–Meier (KM) curves for OS had a corresponding P value = 0.0879. For the cutoff date of February 8, 2021, with a median follow-up of 11.9 months, results of OS were overall consistent with the initial cutoff, with 34 deaths in the cabozantinib arm and 20 deaths in the placebo arm (27% vs. 32% respectively). Median OS was 19.4 (95% CI, 15.9 to NE) months in the cabozantinib group and was not reached (95% CI, NE to NE) in the placebo group. Of note, these results at a later data cutoff were assessed post-hoc, following the primary analysis, and so, are considered supplemental to the primary analysis results.

PFS was a co-primary end point and adjusted for multiplicity. At the data cutoff of August 19, 2020; a total of 74 events were reported. The median follow-up time was 6.24 months. The median PFS was not reached (96% CI, 5.7 to NE) in the cabozantinib arm compared with 1.9 months (1.8 to 3.6) in the placebo arm. The P value obtained from the log-rank stratified test was less than 0.0001. For the cutoff date of February 8, 2021, results of PFS were overall consistent. With a median follow-up time of 11.9 months in the primary analysis population (n = 187), the median PFS was reached at 11.1 months (96% CI, 7.4 to 13.8) in the cabozantinib arm vs. 1.9 months (1.8 to 3.8) in the placebo arm, with a P value obtained from the stratified log-rank test of less than 0.0001, below a critical P value used for testing of 0.00036.

ORR was a co-primary end point in the COSMIC-311 trial and adjusted for multiplicity. In the OITT population, at the cutoff date of August 19, 2020, with a median follow-up time of 5.8 months, the ORR was 15% (99% CI, 5.8 to 29.3) in the cabozantinib group versus 0% (99% CI, 0 to 14.8) in the placebo group (P = 0.028, considered not significant at the prespecified critical value of 0.01). At the cutoff date of February 8, 2021, with a longer median follow-up time (11.9 months), the ORR was 15% (99% CI, 9.4 to 22.7) in the cabozantinib group versus 0% (99% CI, 0 to 5.8) in the placebo group (P = 0.0005).

HRQoL was assessed with the EQ index (a converted normalized measure of the EQ-5D-5L score for different countries) and EQ VAS. In both HRQoL measures, there was immaturity in the data and no evidence of different effects between the 2 arms of the study throughout the length of the study at the end of week 65.

Harms Results

AEs were more prevalent in the cabozantinib group as compared to placebo (166 [98%] vs. 75 [85%] respectively) at the cutoff of February 8, 2021, and included diarrhea (62% vs. 3.4% respectively), palmar plantar erythema syndrome (PPES) (47% vs. 1.1%), hypertension (32% vs. 3.4%), decreased appetite (31% vs. 13%), fatigue (29% vs. 8%), nausea (28% vs. 2.3%), increased liver enzymes (25% vs. 2.3%), hypocalcemia (25% vs. 3.4%), and decreased weight (22 vs. 2.3%).

SAEs at the cutoff date of February 8, 2021 were also more common in the cabozantinib arm (66 patients [39%]) when compared to placebo (24 patients [27%]), and included diarrhea, pleural effusion, pneumonia, pulmonary embolism, and dyspnea. AEs of special

interest also occurred more frequently in the cabozantinib group than in the placebo group, including severe diarrhea (7.6% vs. 0% respectively), thromboembolism (10% vs. 1.1%), hypertension (34% vs. 3.4%), elevated liver enzymes (25% vs. 2.3%), PPES (47% vs. 1.1%), and hypocalcemia (25% vs. 3.4%). There were no treatment-related deaths.

Critical Appraisal

Overall, the COSMIC-311 trial is at low risk of bias. It was a double-blind randomized trial with adequate randomization, concealment allocation, masking, and assessment of outcomes. Some concerns of internal validity remain, arising from the high number of patients who crossed over from the placebo to the intervention group, and the possibility of patients and researchers being aware of the intervention administered due to AEs more commonly observed in the cabozantinib arm (potential unblinding). Overall baseline characteristics were balanced. The authors performed an adequate adjustment for multiplicity in the evaluation of the 2 co-primary end points, ORR and PFS. Other outcomes, including HRQoL, were not adjusted for multiple comparisons. Concerns regarding external validity included the exclusion of patients who had brain metastases or previous radiation therapy for bone metastases. Furthermore, the study had a relatively short period of follow-up (median of 11.9 months at the cutoff date of February 8, 2021) denoting immaturity of the data for estimation of OS. Interpretation of the OS data is also limited by the sample size and crossover of patients from placebo to open-label cabozantinib. There is a gap in the overall body of evidence since no comparative efficacy or harms data were available for comparators of interest in the Canadian clinical context, such as selpercatinib or larotrectinib, which are used in the targeted mutation settings.

Indirect Comparisons

No indirect treatment comparisons were included in this report.

Other Relevant Evidence

No other relevant evidence was included in this report.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with locally advanced or metastatic differentiated thyroid carcinoma that have progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapies and who are radioactive iodine-refractory (RAI-R) ineligible
Treatment	Cabozantinib with best supportive care (BSC; consisting of analgesia, antibiotics for infections, transfusions for anemia, nutritional support, and psychological support with medication or counseling as appropriate)
Dose regimen	60 mg orally once daily

Component	Description
Submitted price	Cabozantinib, 20 mg, 40 mg, and 60 mg, oral tablet: $301.29 per tablet
Treatment cost	$8,436 per 28-day cycle
Comparator	BSC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	COSMIC-311
Key limitations	• There was uncertainty in the generalizability and long-term effects (OS and PFS) of cabozantinib treatment based on the COSMIC-311 clinical trial due to a selective patient population (i.e., exclusion of bone metastasis patients, inclusion criteria of ECOG performance score of 0 or 1 patients only) and a short follow-up period (median follow-up of 11.9 months [February 8, 2021 data cut]). • The COSMIC-311 trial protocol allowed crossover in the placebo arm and adjustments were made using the rank preserving structural failure time method to inform the OS curves of the BSC arm within the economic model. Although assumptions for crossover adjustment analyses would generally result in a conservative underestimate of the comparative treatment effect for cabozantinib to BSC, there is inherent uncertainty associated with this methodology that is further propagated into the economic model. • Clinical experts consulted by CADTH noted that the utility value used by the sponsor to inform the progression-free health state for RAI-R DTC patients (0.87) was likely overestimated, biasing in favour of cabozantinib. Age-adjusted utility values were not incorporated into the sponsor's model despite the clinical experts noting that age is expected to impact a patient's quality of life. • Comparative efficacy of cabozantinib to larotrectinib and selpercatinib, in patients with neurotrophic tyrosine receptor kinase (NTRK) gene fusion or rearranged during transfection mutation-positive DTC that have progressed following prior VEGFR-targeted therapy and are RAI-R were not available; therefore, cost-effectiveness of cabozantinib to these comparators is unknown.
CADTH reanalysis results	• CADTH undertook the following changes to address some of the identified key limitations as part of its reanalysis: selecting alternative parametric curves for OS and PFS for cabozantinib and OS for BSC; selecting an alternate source to inform utility values; and applying age-adjusted utility values. • In the CADTH reanalysis, the ICER for cabozantinib plus BSC was $664,742 per QALY compared to BSC alone. Price reductions of at least 95% would be required for cabozantinib, or for cabozantinib plus BSC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY threshold. • The results were driven by the model being sensitive to the expected OS benefit with cabozantinib. The CADTH reanalysis estimated a smaller OS benefit compared to the sponsor's base-case analysis, although uncertainty remains as to the expected magnitude of the OS benefit modelled, given the OS data were immature in the COSMIC-311 trial.

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; LY = life-year; NTRK = neurotrophic tyrosine receptor kinase; OS = overall survival; PFS = progression-free survival; QALY= quality-adjusted life-year; RAI-R = radioactive iodine-refractory; VEGFR = vascular endothelial growth factor receptor.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the expected market share for cabozantinib was likely underestimated; and the number of patients who would be eligible for public funding of cabozantinib is expected to be higher than the sponsor's estimates. The CADTH reanalysis updated the market share for cabozantinib to reflect an uptake of 55%, 65%, and 75% in year 1, year 2, and year 3, respectively. In the CADTH base-case analysis, the 3-year budget impact of reimbursing cabozantinib is $23,209,107 ($6,252,383 in year 1, $7,699,525 in year 2, and $9,257,199 in year 3). The estimated budget

impact is highly sensitive to the proportion of patients with RAI-R DTC who would receive cabozantinib.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: September 14, 2022.

Regrets: Three expert pERC members did not attend.

Conflicts of interest: None.