Canada's
Drug and Health
Technology Agency

CADTH Health Technology Review

Vandetanib (Caprelsa) for Medullary Thyroid Cancer

CADTH's Provincial Advisory Group, in collaboration with the Canadian Association of Provincial Cancer Agencies' Supply Disruption Working Group, requested that CADTH conduct a clinical review of the evidence on alternative treatment options for patients with medullary thyroid cancer. While the vandetanib 100 mg and 300 mg shortages have been avoided, CADTH published this report in the event of a future vandetanib supply shortage.

Drug Implementation Advice

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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.

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Abbreviations

AE	adverse events
AMSTAR 2	A MeaSurement Tool to Assess Systematic Reviews 2
CI	confidence interval
CR	complete response
DOR	duration of response
DP	disease progression
DTC	differentiated thyroid cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Association for Medical Oncology
HAS	Haute autorité de santé
HTA	health technology assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LD	longest diameter
MTC	medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
SAE	serious adverse events
SMC	Scottish Medicines Consortium
SD	stables disease

SR	systematic review
TC	thyroid cancer
TKI	tyrosine kinase inhibitor

What Is the Unmet Need?

Around 3% to 5% of thyroid cancer is medullary thyroid cancer (MTC). Of these, 25% are inherited and 75% to 80% are sporadic. Ninety-eight percent of inherited MTC and 6% to 10% of sporadic MTC test positive for a germline rearranged during transfection (*RET*) mutation, whereas about 50% of sporadic MTC detect for somatic *RET* mutation [1-5] Vandetanib is the standard of care currently funded in Canada and indicated for the treatment of symptomatic or progressive MTC in adult patients with unresectable locally advanced or metastatic disease.[6] Although selpercatinib is the only other drug approved in Canada for the treatment of MTC, it is indicated for a subset of patients with MTC; that is, *RET*-mutant MTC in adult and pediatric patients 12 years and older with unresectable advanced or metastatic disease.[7] Selpercatinib for *RET*-mutant MTC underwent a CADTH reimbursement review and is awaiting a final recommendation.[5] In the event of a vandetanib 100 mg supply shortage there will be an unmet need for treatment for patients with MTC.

How Did CADTH Approach This Review?

CADTH's Provincial Advisory Group, in collaboration with the Canadian Association of Provincial Cancer Agencies' Supply Disruption Working Group, requested that CADTH conduct a clinical review of the evidence on alternative treatment options for patients with MTC. Although the vandetanib 100 mg and 300 mg shortages have been avoided, the aim of this CADTH report was to synthesize the evidence on the efficacy and safety of alternative treatment options for MTC and inform decision-making on what treatment options are preferred for use in the event of a supply shortage of vandetanib 100 mg. The within-scope alternative treatment options for MTC include cabozantinib, selpercatinib, pralsetinib, sunitinib, lenvatinib, sorafenib, and pazopanib. CADTH convened an implementation advice panel that captured expert advice through consensus on the preferred treatment options to use in the *RET*-mutant and non–*RET*-mutant populations in the event of a vandetanib 100 mg supply shortage. The panel did not assess any economic evidence associated with the alternative treatment options, nor did it identify how alternative treatment options will be accessed.

The implementation advice outlined in this report is only applicable in the event of a vandetanib 100 mg supply shortage.

What Are the Limitations of the Review?

Information was synthesized across different sources, including product labels, health technology assessments (HTAs), and systematic reviews. There was also significant heterogeneity between the included studies in the systematic reviews, which makes it difficult to compare the drugs and outcomes using the available evidence.

Implementation Advice

The panel included 5 medical oncologists from across Canada: 2 medical oncologists specialized in the treatment of MTC, 1 pharmacist, and 1 ethicist. The panel met on June 1, 2022, with the aim of achieving consensus on the preferred treatment options to use for patients with *RET*-mutant and non–*RET*-mutant MTC in the event of a supply shortage of vandetanib 100 mg in Canada.

The panel provided implementation advice on prescribing of alternative treatment options for those with *RET*-mutant and non–*RET*-mutant MTC. Table 1 outlines the list of implementation issues and advice, as well as the corresponding rationale. This is followed by evidence considered by the panel to support the rationale for the implementation advice. Figure 1 illustrates the prescribing of alternative treatment options for MTC.

Table 1: Implementation Issues, Advice, and Rationale

Implementation issues	Implementation advice and rationale
***RET*-mutant MTC**	
Treatment options for *RET*-mutant MTC	
Based on current clinical practice for MTC, which treatment options should be considered for patients with *RET*-mutant MTC? If patients with *RET*-mutant MTC are unable to access selpercatinib, what alternative treatment options would be considered?	Implementation advice *RET* testing is desirable to have available for jurisdictions across Canada to identify eligible patients. Targeted therapy is recommended for patients with *RET*-mutant MTC. Based on the existing Health Canada NOC of selpercatinib for *RET*-mutant MTC, selpercatinib is suggested as a first treatment option. If selpercatinib is unavailable, then pralsetinib may be considered followed by cabozantinib or vandetanib 300 mg if available. **Rationale** Selpercatinib is indicated for *RET*-mutant MTC by Health Canada, the EMA, and the FDA. Pralsetinib is indicated for *RET*-mutant MTC by the FDA. Though the studies (LIBRETTO-001 and ARROW) had a small patient population, the data appear to have good biological rationale, and efficacy data are positive. Based on clinical experience in other tumors, selpercatinib and pralsetinib are relatively well tolerated compared to cabozantinib. Health Canada recommends that treatment with selpercatinib only be initiated following confirmation of a *RET* gene fusion or mutation using a validated test.[7] The availability of *RET* testing is inconsistent across Canada. Before selpercatinib or pralsetinib, vandetanib was used in the treatment of MTC (*RET* mutant or not). Vandetanib and cabozantinib were noted to have similar efficacy profiles

Implementation issues	Implementation advice and rationale
	based on the pivotal EXAM and ZETA trials, respectively (refer to Appendix 4). The EXAM trial for cabozantinib included 48.1% patients with *RET*-mutant MTC. According to the product monograph, vandetanib has serious warnings and precautions related to QTcF interval prolongation, heart failure (fatal), hypertension (grade 4), or hypertensive crisis. Therefore, prescribing and dispensing vandetanib should be carefully considered through the Restricted Distribution Program.[6]
Non–*RET*-mutant MTC	
Treatment options for non–*RET*-mutant MTC	
Based on current clinical practice for MTC, which treatment options should be considered for patients with non–*RET*-mutant MTC? To preserve the vandetanib supply for existing patients, and when new enrolments are ineligible for vandetanib, in what order should these alternative treatment options be provided?	Implementation advice For new enrolments with non–*RET*-mutant MTC, cabozantinib is the preferred treatment option with due consideration for dosing. If cabozantinib is unavailable, lenvatinib would be considered an acceptable treatment option. **Rationale** Vandetanib and cabozantinib were noted to have a similar efficacy profiles based on the EXAM and ZETA trials, respectively (refer to Appendix 4). Cabozantinib's efficacy profile is based on a phase III study in those with non–*RET*-mutant MTC and the panel identified this drug as the most preferred treatment option for non–*RET*-mutant MTC among the alternative options. Although the FDA-approved dose for MTC is the 140 mg capsule formulation used in the EXAM trial, the panel suggested the use of a 60 mg dose (tablet formulation) of cabozantinib (as the maximum dose), which is a formulation available in Canada (other strengths are 20 mg and 40 mg tablets). Further, clinical trials have reported higher adverse events and related rates of drug discontinuation with cabozantinib 140 mg capsules (refer to Panel Consideration 4e). Lenvatinib's efficacy profile is based on a phase II study in patients with MTC. The panel considered the toxicity of lenvatinib to be acceptable, based on members clinical experience with regards to its use in differentiated thyroid cancer. Response rates and PFS outcomes appear comparable between cabozantinib and lenvatinib (refer to Appendix 7). The panel noted that pazopanib and sorafenib were the least preferred treatment options for MTC based on their activity and toxicity compared to cabozantinib. Switching patients who are responding to a current treatment may be harmful. Therefore, it is preferable to preserve the supply of vandetanib 300 mg for existing patients who are already initiated on vandetanib 300 mg.

Implementation issues	Implementation advice and rationale
Prescribing considerations for existing patients with non–*RET*-mutant MTC currently treated with vandetanib 200 mg or 100 mg	
For existing patients with MTC who have been responding to a reduced dose of 200 mg or 100 mg vandetanib, what alternative treatment options should be provided to patients in the event of a supply shortage of 100 mg vandetanib?	Implementation advice For existing patients with MTC who have been responding to a reduced vandetanib daily dose of 200 mg or 100 mg, an alternate dosing schedule using vandetanib 300 mg or cabozantinib would be considered as the next available treatment options. If cabozantinib is unavailable, lenvatinib would be considered an acceptable treatment option. The starting dose (reduced or full) of cabozantinib or lenvatinib will depend on the individual patient's toxicities. **Rationale** The alternate dosing schedule of vandetanib 300 mg in this patient population was suggested based on the long half-life (19 days), time to achieve peak plasma concentration (average of 6 hours), and steady state achieved in approximately 3 months. In addition, clinicians' choice of TKI will depend on the patient's tumour response and adverse events. It is also a common practice to put the medication on hold for a limited time when patients on a TKI experience intolerable adverse effects. Cabozantinib and lenvatinib have reasonable safety and efficacy profiles in patients with non–*RET*-mutant MTC. Given the dose-response relationship of TKIs, the maximum approved and tolerated doses are generally recommended. With respect to toxicity, patients may have varied levels of tolerance for different TKIs. The panel noted that a reduced dose of 1 TKI may not necessitate a reduced dose of another TKI. Of note, switching between drugs without a washout period may overlap toxicities of the 2 drugs. Based on clinical experience, MTC generally does not progress aggressively, which may allow time for a washout period under careful clinical observation.
Prescribing considerations for existing patients with non–*RET*-mutant MTC and currently treated with vandetanib 300 mg but need a dose reduction	
If a patient is receiving 300 mg of vandetanib and experiences a treatment-related toxicity that requires a dose reduction to 200 mg or 100 mg daily, in the event of a supply shortage of the 100 mg vandetanib, what alternative treatment options should be considered?	Implementation advice If a patient is receiving 300 mg of vandetanib and experiences a treatment-related toxicity that requires a dose reduction to 200 mg or 100 mg daily, vandetanib 300 mg on an alternate dosing schedule is suggested as a first option. If vandetanib 300 mg supply on an alternate dosing schedule is unavailable, dose-reduced or full-dose cabozantinib would be considered next. If cabozantinib is unavailable, lenvatinib would be considered an acceptable treatment option. **Rationale** The alternate dosing schedule of vandetanib 300 mg in this patient population was suggested based on the long half-life (19 days), time to achieve peak plasma concentration (average

Implementation issues	Implementation advice and rationale
	of 6 hours), and steady state achieved in approximately 3 months. In addition, clinicians' choice of TKI will depend on the patient's tumour response and adverse events. It is also a common practice to put the medication on hold for a limited time when patients on a TKI experience intolerable adverse effects. Cabozantinib and lenvatinib have acceptable safety and efficacy profiles in non–*RET*-mutant MTC. Given the dose-response relationship of TKIs, the maximum approved and tolerated doses are generally recommended. With respect to toxicity, patients may have varied levels of tolerance for different TKIs. The panel noted that a reduced dose of 1 TKI may not necessitate a reduced dose of another TKI. Of note, switching between drugs without a washout period may overlap toxicities. Based on clinical experience, MTC generally does not progress aggressively, which may allow time for a washout period under careful clinical observation. Clinicians prescribing TKIs generally need to go through a rigorous prescriber program. Hence, these prescribers would be highly experienced in side effect management and alternate dosing strategies of TKIs.
If a patient receiving vandetanib switches to an alternate therapy in the event of a 100 mg vandetanib shortage, when the 100 mg tablet becomes available again, do these patients continue with the current therapy until treatment progression or switch back to vandetanib?	Implementation advice In the event of a 100 mg vandetanib shortage, a patient receiving an alternate drug of cabozantinib or lenvatinib should continue on this treatment if well tolerated, disease is controlled, and toxicity is acceptable. If cabozantinib or lenvatinib is not tolerated or there is disease progression while receiving the alternate drug, then switching back to treatment with vandetanib is suggested. **Rationale** The panel agreed that if a patient is responding to treatment and has acceptable toxicity, treatment should be continued.

EMA = European Medicines Agency; MTC = medullary thyroid carcinoma; NOC = Notice of Compliance; PFS = progression-free survival; QTcF = corrected QT interval by Fredericia; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor.

Panel Considerations

The rationale for the panel's implementation advice is supported by the following evidence, as well as ethical and other considerations.

1. Vandetanib
    a. Vandetanib has Health Canada Notice of Compliance for MTC that is based on the pivotal ZETA study. This phase III, multicentre, international, randomized, double-blind, placebo-controlled, parallel group study assessed the efficacy and safety of 300 mg daily oral dose of vandetanib (n = 231) compared to placebo (n = 100) in patients with unresectable locally advanced or metastatic MTC.[6]
    b. In Canada, vandetanib is only available through a Restricted Distribution Program. As outlined in this program, prescribers and pharmacies must

complete the certification and be registered with the program to prescribe and dispense vandetanib, respectively. All patients receiving vandetanib need to be enrolled and meet the criteria of the Restricted Distribution Program.[6]

c. The half-life of vandetanib is 19 days.[6] The time to achieve peak plasma concentration is 6 hours (range = 4 to 10 hours), and there is approximately an 8-fold accumulation on multiple dose with steady state achieved in approximately 3 months.[9] Once steady state is achieved, an alternate dosing schedule of vandetanib 300 mg may be considered, depending on patient's tolerance for drug toxicity and clinical circumstances. The alternate dosing of vandetanib 300 mg was suggested based on panel members' clinical experience with other tyrosine kinase inhibitors (TKIs) in other tumours.

2. Selpercatinib

   a. Selpercatinib has Health Canada Notice of Compliance for *RET*-mutant MTC, which is based on an ongoing study (LIBRETTO-001). This open-label, multicentre, multicohort phase I and II trial assessed the efficacy and safety of selpercatinib in patients with advanced solid tumours, with *RET* activations. Efficacy data from 2 subgroups were considered for the approval; patients with metastatic *RET*-mutant MTC previously treated with vandetanib or cabozantinib (n = 55), and patients with vandetanib- and cabozantinib-naive metastatic *RET*-mutant MTC (n = 88).[10]

      Key end points (refer to Appendix 4 for further details on efficacy and safety data):

      i. Patients previously treated with vandetanib or cabozantinib or both (n = 55)

         Objective response rate (ORR) = 69% (95% confidence interval [CI], 55 to 81); complete response (CR) = 9.1%; partial response (PR) = 60%

         Duration of response (DOR): median duration of follow-up =14.1 months; patients with response = 38; DOR events = 6; median DOR = non-evaluable (95% CI, 19.1 to non-evaluable)

         Progression-free survival (PFS): median duration of follow-up = 16.7 months

      ii. Patients naive to vandetanib and cabozantinib (n = 88)

         ORR = 73% (95% CI, 62 to 82) ; CR = 11% ; PR = 61%

3. Pralsetinib

   a. Pralsetinib has a Health Canada Notice of Compliance for non–small cell lung cancer that is based on the ARROW study. The approved dosage is 400 mg once daily. Only the FDA has approved the use of pralsetinib in *RET*-mutant MTC thus far.[11,12]

   b. The FDA approval of pralsetinib in *RET*-mutant MTC is based on the pivotal ARROW study. This open-label, non-randomized, multicentre, multicohort phase I and II trial assessed the efficacy and safety of pralsetinib in patients with thyroid cancer, non–small cell lung cancer, and other advanced solid tumours. Efficacy data from 2 subgroups were considered for the approval; patients with *RET*-mutant MTC previously treated with vandetanib or cabozantinib (n = 55) and patients with vandetanib- and cabozantinib-naive *RET*-mutant MTC (n = 29).[11]

Key end points (refer to Appendix 4 for further details on efficacy and safety data):

i. Patients previously treated with cabozantinib or vandetanib (n = 55)

ORR = 60% (95% CI, 46 to 73); CR = 1.8%; PR = 58%

Patients with DOR of 6 months or longer[h] = 79%

ii. Patients with cabozantinib- and vandetanib-naive *RET*-mutant MTC (n = 29)

ORR = 66% (95% CI, 46 to 82); CR = 10%; PR = 55%

Patients with DOR of 6 months or longer = 84%

4. Cabozantinib

a. Cabozantinib has Health Canada Notice of Compliance for renal cell carcinoma, hepatocellular carcinoma (HCC), and differentiated thyroid cancer (DTC). The approved dosage is 60 mg once daily (tablet formulation), with possible dose reduction to 40 mg and 20 mg (tablet formulation) to manage toxicity.[10] Only the FDA and the European Medicines Agency (EMA) have approved the use of cabozantinib in MTC.[13,14]

b. The FDA and EMA approval of cabozantinib in MTC is based on the pivotal EXAM trial. This phase III, multicentre, international, randomized, double- blind, placebo-controlled study assessed the safety and efficacy of cabozantinib 140 mg per day (capsule formulation) in 330 patients (cabozantinib = 219; placebo = 111) with unresectable, locally advanced, metastatic, and progressive MTC.[13,14]

Key end points (refer to Appendix 4 for further details on efficacy and safety data):

i. Median PFS: cabozantinib = 11.2 months versus placebo = 4 months. Absolute gain of 7.2 months in favour of cabozantinib (hazard ratio [HR] = 0.28; 95% CI, 0.19 to 0.40; P < 0.0001), with a median trial follow-up of 13.9 months.

ii. Median overall survival (OS): cabozantinib = 26.6 months versus placebo = 21.1 months. Not statistically significant (HR = 0.85; 95% CI, 0.64 to 1.12), with a median trial follow-up of 52 months.

c. Based on an indirect treatment comparison and expert opinion, the National Institute for Health and Care Excellence's (NICE's) HTA concluded that cabozantinib and vandetanib are likely to have similar effectiveness in terms of delaying progression and controlling symptoms, but there was no evidence of prolonging survival; and that the choice between the 2 was related more to their differing toxicity profiles than their relative effectiveness (refer to Appendix 4).

d. The effect of cabozantinib may not be as robust in the non–*RET*-mutant population. NICE, the Scottish Medicines Consortium (SMC), and Haute autorité de santé's (HAS's) HTAs note the possibility of lower benefit in patients in whom *RET* mutation status is unknown or negative (refer to Appendix 4).

e. In Canada, cabozantinib is available as 20 mg, 40 mg, and 60 mg tablets, whereas the EXAM trial used the 140 mg capsule, which is not available in

Canada. More than 75% of the patient population needed a dose reduction due to adverse events in the EXAM trial that administered 140 mg per day cabozantinib in patients with MTC. The FDA-approved dose for cabozantinib is 140 mg capsules per day[13,14] (refer to Appendix 4). A phase IV, randomized, double-blind, non-inferiority study comparing 140 mg per day capsules with 60 mg per day tablets concluded that "progression-free survival (PFS) non-inferiority of the cabozantinib 60 mg/day tablet versus 140 mg/day capsules was not met"[15] (p.1). The median PFS for the 60 mg per day tablet arm was 11.0 months compared to 13.9 months for the 140 mg per day arms (HR = 1.24; CI, 0.90 to 1.70; P = 0.19). The ORR was same in both arms (33%). Of note, the percentage of patients with prior TKI therapy was larger in patients receiving cabozantinib 60 mg tablets (56%) than in patients receiving cabozantinib 140 mg capsules (46%). Further, the study concluded that "adverse event (AE) incidence was lower in the 60 mg/day arm (Grade 3/4, 63% vs. 72%), as were dose reductions (69% vs. 81%) and treatment discontinuations due to AEs (23% vs. 36%)"[15] (p.1).

f. For the appropriate assessment of patient's response with respect to toxicities, the following may be considered, depending on a patient's circumstances:

   i. the starting dosing (reduced or full dose) of cabozantinib

   ii. the washout period, if initiating directly with cabozantinib full dose (60 mg per day).

5. Lenvatinib

   a. Lenvatinib has Health Canada Notice of Compliance for DTC, renal cell carcinoma, and HCC. The approved dose range is between 8 mg (HCC) and 24 mg (DTC) per day.[16] In an international phase II clinical trial of lenvatinib in patients with unresectable progressive MTC (n = 59), patients received 28-day cycles of lenvatinib 24 mg per day, until disease progression, unmanageable toxicity, withdrawal, or death. The trial permitted prior anti–vascular endothelial growth factor receptor therapy. ORR was the primary end point.[17]

      i. ORR = 36% (95% CI, 24% to 49%); all PR; ORR was comparable between patients with (35%) or without (36%) prior anti–vascular endothelial growth factor receptor therapy

      ii. Disease control rate = 80% (95% CI, 67% to 89%)

      iii. Stable disease (SD) = 44%

      iv. Among responders, median time to response = 3.5 months (95% CI, 1.9 to 3.7); median PFS = 9.0 months (95% CI, 7.0 to not evaluable)

6. Other discussion points

   a. While there is no anticipated shortage of vandetanib 300 mg, the potential for alternate dosing of vandetanib 300 mg in patients requiring a reduced dose of vandetanib will increase the demand for vandetanib 300 mg.

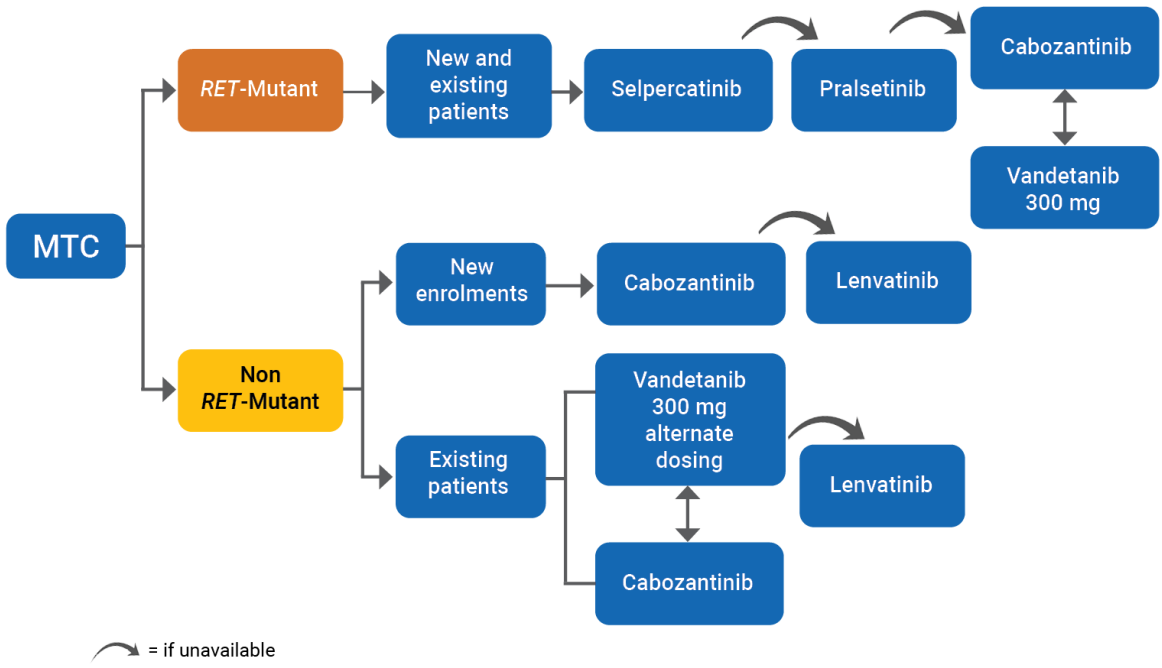
   b. Clinicians prescribing TKIs generally need to go through a rigorous prescriber program and are frequent prescribers of TKIs. Hence, these prescribers would be highly experienced in side effect management and alternate dosing strategies of TKIs.

c. There were concerns raised with access, equity, and affordability by suggesting alternative treatment options for MTC that are not currently funded by public drug plans.

7. Ethical consideration

   a. The Ethical Framework for Resource Allocation During the Drug Supply Shortage (2012) recommends that the first stage is to "Implement strategies to preserve standard of care and best practices to the greatest extent possible within available drug supply" (p. 3). The second stage is to "Apply primary allocation principles to optimize therapeutic benefit" (p. 4). The third stage is to "Apply secondary allocation principles to ensure fair access to needed care" (pg. 5).[18]

Figure 1: Prescribing of Drugs In MTC For New And Existing Patients In the Event of a Vandetanib 100 Mg Shortage



MTC = medullary thyroid carcinoma; RET = rearranged during transfection.
Note: This figure is not a replacement for an algorithm.

Background

Thyroid cancer (TC) is characterized by the development of malignant cells in the tissues of the thyroid gland.[19] Papillary is the most prevalent type of TC and represents 80% to 85% of TC cases, followed by follicular (7% to 15% of TC cases), medullary (3% to 5% of TC cases), and anaplastic (1% to 2% of TC cases). The focus of this CADTH review is on MTC.[2-4]

MTCs are neuroendocrine tumours that originate in the thyroid parafollicular cells (C cells). There are 2 forms of MTC, sporadic and inherited. About 75% to 80% of all MTCs are sporadic, and are often seen in older adults. About 25% of all MTCs are inherited, are usually seen in childhood or early adulthood, and spread more rapidly. Inherited MTC occurs mostly in patients with inherited multiple endocrine neoplasia syndrome.[2,3]

The characteristic feature of MTC is the production of calcitonin. Serum calcitonin and carcinoembryonic antigen are important diagnostic, prognostic, and predictive biomarkers for MTC.[2,3] The most common clinical symptoms associated with MTC are a thyroid nodule; enlarged neck lymph nodes; diarrhea; bumps on lips, eyelids, or tongue; and high-blood pressure.[3] At the time of diagnosis, the majority of MTC cases are already metastasized, with distant metastases occurring in the liver, lungs, bones, and less often in brain and skin. Tumour staging for MTC is based on tumour size and the presence or absence of extrathyroidal invasion, local and regional nodal metastases, and distant metastases. MTC is more common in females than in men.[2-4]

MTC disease pathogenesis involves mutation of the *RET* proto-oncogene, which "encodes a single-pass transmembrane protein receptor, that belong to the receptor tyrosine kinase family"[1](p. 126). About 98% of inherited MTC and 6% to 10% of sporadic MTC test positive for germline *RET* mutation, whereas about 50% of sporadic MTC detect for somatic *RET* mutation.[1-5]

For the treatment of MTC, clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) and European Association for Medical Oncology (ESMO) recommend surgery (total thyroidectomy and dissection of cervical lymph node compartments) as a standard approach for sporadic or inherited MTC, as it is the only curative option for locoregional MTC. In cases of recurrent or residual MTC, NCCN and ESMO guidelines recommend "close observation for indolent disease, surgical resection of locoregional disease, external beam radiation therapy (EBRT), and local therapies, such as radiofrequency ablation, cryoablation, and embolization, or systemic therapies, such as conventional chemotherapy, kinase inhibitors, and immune checkpoint inhibitors for non-resectable diseases" (p. 518).[4] The NCCN and ESMO guidelines also note that "treatment approaches in these patients depend on various clinical factors, including presence of the symptoms, possibility of significant structural disease progression, disease localization, disease volume or burden, and location of the metastatic lesion" (p. 518).[4]

Candidates for systematic therapy include patients with progressive or symptomatic metastatic disease who cannot be treated with surgery or radiotherapy.[20] The mainstay treatment for advanced MTC are TKIs, which are small molecules that target intracellular

signalling pathways at different sites. The NCCN and ESMO guidelines recommend systemic therapy, such as vandetanib or cabozantinib, as first-line regimens in unresectable locoregional diseases and distant metastases with symptomatic or progressive MTCs by Response Evaluation Criteria in Solid Tumors (RECIST).[4] RECIST is a "methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden."[13] In addition, the NCCN recommends other TKIs, including sunitinib, lenvatinib, sorafenib, and pazopanib be considered for MTC.[4] These 4 TKIs can be considered in patients who fail on either or both cabozantinib and vandetanib.[20] The NCCN recommends selpercatinib and pralsetinib, 2 highly selective *RET* inhibitors, for *RET*-mutant MTC only.[4,6,10]

On January 12, 2012, Health Canada issued a Notice of Compliance for vandetanib for the treatment of symptomatic or progressive MTC in adult patients with unresectable locally advanced or metastatic disease.[21] In 2017, Sanofi Genzyme, the manufacturer of vandetanib (Caprelsa), filed a CADTH submission for vandetanib for the treatment of symptomatic and/or progressive MTC in adult patients with unresectable locally advanced or metastatic disease. pERC issued a final recommendation of vandetanib for the treatment of patients who have symptomatic and/or progressive MTC with unresectable locally advanced or metastatic disease and with a good performance status.[22] On June 15, 2021, Health Canada issued a Notice of Compliance for selpercatinib for *RET*-mutant MTC in adult and pediatric patients 12 years and older with unresectable advanced or metastatic disease.[21] In 2022, Eli Lilly Canada Inc. filed a CADTH submission for selpercatinib for *RET*-mutant MTC in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease.[5] Recently, pERC issued a draft recommendation, with conditions, for selpercatinib for the treatment of *RET*-mutant MTC in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease who have progressed on or are intolerant to first-line therapy.[5,22] Appendix 1 outlines the regulatory status of alternative treatment options under consideration for MTC.

CADTH's Provincial Advisory Group, in collaboration with the Canadian Association of Provincial Cancer Agencies' Supply Disruption Working Group, requested that CADTH conduct a clinical review of the evidence on alternative treatment options for patients with MTC. While the vandetanib 100 mg and 300 mg shortages have been avoided, CADTH published this report in the event of a future vandetanib supply shortage.

Research Question

The report addressed the following research question:

What are the efficacy and safety of alternative treatment options in the event of a vandetanib shortage for MTC?

Methods

Literature Search Methods

Published literature was identified by searching the following bibliographic databases: Medline All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were thyroid cancer and small molecule kinase inhibitors sorafenib, sunitinib, pazopanib, and lenvatinib. CADTH-developed search filters were applied to limit retrieval to HTAs, systematic reviews, meta-analyses, or indirect treatment comparisons. Where possible, retrieval was limited to the human population. The search was completed on April 27, 2022, and limited to documents published since January 1, 2017.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature resource: Health Technology Assessment (HTA) Agencies, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, and Drug Class Reviews.[24] Google was used to search for additional internet-based materials.

This report was conducted in accordance with the *Procedures for Review of Therapeutic Alternatives During a Drug Supply Shortage*.

Selection Criteria and Methods

To summarize the evidence on efficacy and safety of the interventions outlined in Table 1 in this review, an expedited approach for gathering information was conducted. First, a grey literature search was conducted on the following 5 regulatory agencies (Health Canada, US FDA, EMA, Australia's Therapeutic Goods Administration, and New Zealand's MedSafe) and 9 HTA agencies (CADTH, Institut national d'excellence en santé et en services sociaux [INESSS], Institute for Clinical and Economic Review, NICE, SMC, HAS, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Pharmaceutical Benefits Advisory Committee, and Pharmaceutical Management Agency) to identify existing HTAs or product labels for drugs with regulatory status for MTC. Efficacy and safety data were extracted from product labels and HTA reports for the interventions outlined in Table 1 that were approved by regulatory agencies and/or assessed by HTA agencies for MTC. For the interventions outlined in Table 1 that were not approved by any regulatory agencies for MTC, safety data were gathered from Health Canada's product monographs for indications other than MTC. For the interventions outlined in Table 1 that were not approved by any regulatory agencies for MTC, a search strategy was conducted to identify published systematic reviews and meta-analyses from bibliographic databases to provide efficacy and safety data. One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and

potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 2: Selection and Eligibility Criteria

Criteria	Description
Population and subgroups	Patients with locally advanced or metastatic MTC **Subgroup:** Those with *RET*-mutant MTC
Interventions	• Cabozantinib • Selpercatinib • Pralsetinib • Sorafenib • Sunitinib • Lenvatinib • Pazopanib
Comparators	• Placebo • Any comparators identified in Interventions
Outcomes	• PFS • OS • ORR • DOR • Quality of life • Safety: Grade 3 and 4 AEs, grade 3 and 4 SAEs, withdrawal due to adverse events, death
Study designs	**Systematic reviews** Grey literatures (HTA reports and product labels) from select national and international regulatory agencies and HTA agencies **Regulatory agencies** • Health Canada, Canada • FDA, US • EMA, Europe • TGA, Australia • Medsafe, New Zealand **HTA agencies** • CADTH, Canada • INESSS, Canada • ICER, US • NICE, UK • SMC, UK • HAS, France • IQWiG, Germany • PBAC, Australia • PHARMAC, New Zealand

AE = adverse events; DOR = duration of response; EMA = European Medicines Agency; HAS = Haute autorité de santé; HTA = health technology Assessments; ICER = Institute for Clinical and Economic Review; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen MTC = medullary thyroid carcinoma; NICE = National Institute for Health and Care Excellence; ORR = objective response rate; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression-free survival; TGA = Therapeutic Goods Administration; PHARMAC = Pharmaceutical Management Agency; *RET* = rearranged during transfection; SAE = serious adverse events; SMC = Scottish Medicines Consortium.

Critical Appraisal of Individual Studies

The included publications were critically appraised by a single reviewer using the following tool as a guide: A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2).[25] Additional details regarding the strengths and limitations of the included publication are provided in Appendix 2.

Relevance

The research question and inclusion criteria for the review included components of population, intervention, comparators, and outcomes that were relevant to the current report. Two out of the 3 reviews had a broader inclusion criterion than this present review, either in terms of the interventions included or the diseases studied.[1,26] It is not clear if the broader criteria impacted the overall results.

Credibility

Only 1 systematic review had its review methods established and registered.[1] It was unclear if the review methods were established a priori for the other 2 systematic reviews.[26,27] A comprehensive search to identify eligible studies was conducted in all of the systematic reviews, using multiple electronic databases. Key search words and search strategies were reported by all 3 systematic reviews.[1,26,27] Two systematic reviews searched for studies published until 2018,[1,27] and 1 systematic review searched for studies in 2019.[26] Hence, any studies published after 2019 would not be included. Selpercatinib is not included in any of the systematic reviews. All of the systematic reviews provided a list of excluded studies and the rationale for their exclusion.[1,26,27] Two systematic reviews assessed publication bias.[26,27] In 1 systematic review, it was unclear whether publication bias was examined.[1] Quality assessment of the studies was performed by only 1 systematic review.[1]

Study selections were done by 2 reviewers, independently in 2 systematic reviews, lowering the risk of missing studies.[26,27] Data extraction from the included studies was done by 2 reviewers, independently in 2 systematic reviews, ensuring the relevant study characteristics and outcomes are reported.[1,27] In 1 systematic review it was unclear if study selection was done in duplicates.[1] In 1 systematic review it was unknown if data extraction was done in duplicates.[26] One systematic review noted that there were no funding sources to declare.[1] Two systematic reviews did not declare funding sources or lack thereof.[26,27]

Risk of bias assessment of the included studies was not performed, and neither was its potential impact assessed or discussed in interpreting the results in any of the 3 systematic reviews.[1,26,27]

Analysis

The systematic reviews used meta-analysis to combined the findings on each drug. The methods for statistical combination of results were explained, and the statistical tools used were identified by the 3 systematic reviews. Heterogeneity was calculated using

Cochrane's Qx^2 test[1] and I^2 statistic.[1,26,27] One systematic review used the DerSimonian and Laird method to estimate the summarized effect size in each subanalysis.[1]

Reporting Quality

The reporting quality of the included review was good. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagrams were used to show the study selection process, and forest plots were used by 2 systematic reviews to report on outcomes.[1,27] All results in all 3 of the systematic reviews were reported along with appropriate measures of uncertainty (95% CI) and heterogeneity (I^2). Overall conclusions were presented with consideration of the limitations.[1,26,27]

Conflicts of Interest

Conflicts of interest were declared or declaration of no conflict of interest were reported in all 3 systematic reviews.[1,26,27]

Summary of Evidence

Description of Studies

Summary of Grey Literatures (Product Labels and HTA Reports)

The FDA and the EMA have issued regulatory approval for the use of cabozantinib in adult patients with progressive, unresectable locally advanced or metastatic MTC.[13,14] The FDA has issued regulatory approval for the use of pralsetinib for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy.[11] Health Canada, the FDA, and the EMA have approved the use of selpercatinib as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.[10,20,28] Health Canada has approved cabozantinib, sunitinib, pazopanib, sorafenib, or lenvatinib for indications other than MTC.[16,29-32] Appendix 1 provides further details on regulatory status for cabozantinib, sunitinib, sorafenib, pazopanib, lenvatinib, pralsetinib, and selpercatinib for MTC. Appendix 3 provides information on the mechanism of action for these TKIs, and their approved dosage and formulations.

NICE, SMC, HAS, and IQWiG assessed the use of cabozantinib and selpercatinib for MTC.[3,33-39] While NICE and HAS have recommended cabozantinib for progressive, unresectable locally advanced or metastatic MTC with certain clinical and economic conditions, SMC did not recommend the use of cabozantinib for MTC. NICE, SMC, and HAS have recommended the use selpercatinib for *RET*-mutant MTC, but only on an "interim basis" (SMC), under "managed access agreement" (NICE), or on a "conditional" basis (HAS). As more data become available, NICE, SMC, and HAS will review use of selpercatinib in *RET*-mutant MTC for continued access.[33-38] Additionally, CADTH issued a

draft recommendation on selpercatinib for the treatment of *RET*-mutant MTC in adult and pediatric patients 12 years and older with unresectable advanced or metastatic disease who have progressed on or are intolerant to first-line therapy.[5] Given that documents related to IQWiG's assessment of cabozantinib and selpercatinib are published in the German language, and this CADTH review is limited to English-language only, further details on IQWiG's assessment are unavailable.[3,39] Sunitinib, pazopanib, sorafenib, pralsetinib, or lenvatinib have not been reviewed by CADTH, Institut national d'excellence en santé et en services sociaux (INESSS), NICE, SMC, HAS, IQWiG, Pharmaceutical Benefits Advisory Committee, or Pharmaceutical Management Agency for use in MTC. Appendix 1 provides the clinical rationales of the recommendations issued by the various HTA agencies for the use of cabozantinib and selpercatinib in MTC.

The regulatory approval and HTA for cabozantinib is based on one phase III, multicentre, international, placebo-controlled randomized controlled trial in patients with unresectable, locally advanced metastatic and progressive MTC (EXAM).[14,33,35,37,40] The regulatory approval and HTA for selpercatinib is based on an ongoing single-arm, open-label, multicentre phase I and II trial in people with advanced solid tumours, with *RET* activations (LIBRETTO-001).[5,10,20,28,34,36,38] The expected completion date for the LIBRETTO-001 study is November 21, 2023.[41] There is also an ongoing phase III study, J2G-MC-JZJB (LIBRETTO-531), comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, *RET*-mutant MTC. The expected completion date for the LIBRETTO-531 study is November 13, 2026.[42] The regulatory approval of pralsetinib is based on one phase I and II, multicentre, international, non-randomized, open-label, multi- cohort study in patients with *RET*-mutant MTC (ARROW).[11] The characteristics and results of the pivotal study are presented in Appendix 4.

Summary of Literature Search

As none of the regulatory or HTA agencies have reviewed sunitinib, pazopanib, sorafenib, or lenvatinib for use in patients with MTC, a literature search was conducted to identify published systematic reviews and meta-analyses to report efficacy and safety data on these drugs.

Quantity of Research Available

A total of 82 citations were identified in the literature search. Following screening of titles and abstracts, 76 citations were excluded, and 6 potentially relevant literatures were retrieved for full-text review. Of these 6 potentially relevant articles, 3 were excluded for various reasons. Of the 3 excluded systematic reviews, 1 was a summary article, the second was an observational study, and the third did not include sunitinib, pazopanib, sorafenib, or lenvatinib. Appendix 5 presents the PRISMA flowchart of the study selection.[43]

Summary of Study Characteristics

Three systematic reviews were included in this review.[1,26,27,44]

Two out of the 3 reviews had a broader inclusion criterion than this present review, either in terms of the interventions included or the diseases studied. One systematic review also considered interventions outside the scope of this review (e.g., axitinib, dovitinib).[1] Another systematic review included patients with different types of TC (i.e., DTC, anaplastic TC).[26] Only the characteristics and results that meet the inclusion criteria in Table 1 are summarized in the following text. Funding sources were not declared in any of the 3 systematic reviews.[1,26,27] Appendix 6 presents detailed characteristics of the included publications.

Study Design

All included publications were systematic reviews and meta-analysis. The search strategies were comprehensive, including a search of multiple databases (e.g., PubMed, Scopus, clinicaltrials.gov, Medline, Embase). All publications were conducted following PRISMA. Two systematic reviews searched for studies published until 2018,[1,27] and 1 systematic review searched for studies until 2019.[26] Eligible primary studies in all 3 publications were limited to randomized controlled trials as well as retrospective and prospective studies. Case reports, reviews, and conference proceedings were excluded by all.[1,26,27] One systematic review did not apply any language limitation,[1] while another was limited to English-language only.[26]

The number of primary studies included in the systematic reviews ranged from 8 to 34, and the number of primary studies that met the inclusion criteria specified in Table 1 ranged from 8 to15.[1,26,27] There was overlap in included primary studies across the systematic reviews that assessed sorafenib[1,26,27] and lenvatinib.[1,26]

Country of Origin

The systematic reviews were authored by reviewers from Greece[1] and Japan.[26,27]

Patient Population

The population of interest in all studies was patients with progressive disease (PD) or locally advanced or metastatic MTC.[1,26,27] However, 1 study also included patients with DTC and anaplastic TC.[26] Age limit (> 18 years of age) was specified in only 1 systematic review.[26] Among the included systematic reviews, the total number of patients with MTC ranged from 101 to 600. The population's median age (ranging from 48 to 64 years) and Eastern Cooperative Oncology Group (ECOG) status (ranging from 0 to 1 to 0 to 2) at baseline in the primary studies was reported by 2 systematic reviews.[26,27] One systematic review did not report on median age or ECOG status.[1]

Intervention and Comparators

One systematic review assessed cabozantinib, sunitinib, pazopanib, sorafenib, lenvatinib, axitinib, dovitinib, imatinib, motesanib, and vandetanib.[1] One systematic review only assessed sorafenib,[27] and 1 considered sorafenib, levantinib, vandetanib, and

cabozantinib.[26] All the randomized controlled trials (primary studies) included in the 3 systematic reviews were placebo controlled, and none of them conducted a head-to-head comparison between TKIs. Only 2 systematic reviews noted the doses used, which are the standard dosages of the cabozantinib (140 mg once daily), lenvatinib (300 mg once daily), and sorafenib (400 mg twice daily).[26,27]

Outcomes

All of the systematic reviews used the RECIST criteria to evaluate the tumour response to the treatment.[4] RECIST is a "methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden."[13] CR, PR, and SD were outcomes assessed in all 3 systematic reviews.[1,26,27] One systematic review assessed objective response (OR), which was a combination of CR and PR.[1] PFS was reported in 2 systematic reviews.[1,26] OS was reported in 1 systematic review [26] and disease progression (DP) was reported in 1 systematic review.[1]

Pooled percentages of the response rates were calculated for all interventions in all 3 systematic reviews,[1,26,27] except for 1 systematic review that noted that a meta-analysis could not be performed on lenvatinib and cabozantinib due to the limited number of studies.[26] Heterogeneity among the studies were calculated using the I^2 statistics. Generally, an I^2 more than 50% was considered to be high or significant heterogeneity.[1,26,27]

Efficacy Results

The clinical effectiveness of cabozantinib, pralsetinib, selpercatinib, sunitinib, pazopanib, sorafenib, or lenvatinib are summarized in the following.

Data on the efficacy of cabozantinib, pralsetinib, and selpercatinib are based on the product labels and HTA reports[10,11,33-38,44,45] (refer to Appendix 4). Data on the efficacy of sunitinib, pazopanib, sorafenib, or lenvatinib were gathered from the 3 systematic reviews and meta-analyses.[1,26,27] Appendix 7 presents the efficacy results on these 4 TKIs.

Cabozantinib

Clinical effectiveness: Compared to placebo, cabozantinib estimated an absolute gain of 7.2 months in median PFS (HR = 0.28; 95% CI, 0.19 to 0.40; P < 0.0001), with a median trial follow-up of 13.9 months. The HTA agencies concluded that there was no statistically significant difference in PFS between cabozantinib and placebo in patients with a negative *RET* status. Therefore, HTA agencies have considered a lower benefit of cabozantinib in patients in whom *RET* mutation status is negative or not known.[29,33,35,37]

No statistically significant difference was observed in terms of OS between cabozantinib and placebo.[29,33,35,37] Of note, NICE's assessment group concluded that cabozantinib and vandetanib are "likely to be similarly effective" (p. 8-9) based on an indirect treatment comparison and clinical expert opinion.[33]

Selpercatinib

All HTA agencies have highlighted that the evidence for selpercatinib is highly uncertain because it is based on an ongoing single-arm trial. In this ongoing phase I and II study, there were 2 subgroups of *RET*-mutant MTC. In the subgroup of patients with previously treated patients with *RET*-mutant MTC, selpercatinib was associated with an ORR of 69% (95% CI, 55 to 81). Median DOR and PFS were non-evaluable in this subgroup. The ORR in patients naive to treatment was 73% (95% CI, 62 to 82). This analysis was conducted by an independent review committee. The data cut-off for this primary analysis was December 16, 2019.[10,34,36,38]

Pralsetinib

In this phase I and II study, there were 2 subgroups of *RET*-mutant MTC. In the subgroup of patients previously treated with cabozantinib or vandetanib, pralsetinib was associated with an ORR of 60% (95% CI, 46 to 73). The proportion of patients with CR and PR were 1.8% and 58%, respectively. The median DOR could not be reached. The proportion of patients with DOR of 6 months or more was 79%, based on observed DOR. In the subgroup of patients naive to treatment, pralsetinib was associated with an ORR of 66% (95% CI, 46 to 82). The proportion of patients with CR and PR were 10% and 55%, respectively. The median DOR could not be reached. The proportion of patients with DOR of 6 months or more was 84%, based on observed DOR. The ORR analysis was conducted by a blinded independent central review.[11]

Systematic Reviews: Cabozantinib, Sunitinib, Pazopanib, Lenvatinib, and Sorafenib

Out of the 2 systematic reviews that included studies on cabozantinib, 1 included 1 phase I and 1 phase III study[1], and 1 included 1 phase III study. [26] Two systematic reviews have reported on the PFS data for cabozantinib.[1,26] Out of the 2, 1 systematic review noted that meta-analysis could not be performed on cabozantinib due to the limited number of studies. This systematic review reported the median PFS from a phase III trial (pivotal trial), and noted that the median PFS for cabozantinib was 11.20 months (HR = 0.28; 95% CI, 0.19 to 0.40; P < 0.01) and that of vandetanib was 31 months (pooled analysis; 95% CI, 19 to 43; I^2 = 0%; P < 0.01).[26] One systematic review also reported on OR (CR and PR), overall DP, and SD for cabozantinib.[1]

Only 1 systematic review reported on sunitinib; it included 2 phase II studies on the drug. PFS, OR, and SD were based on pooled analysis.[1]

Only 1 systematic review reported on pazopanib based on 1 phase II study that assessed OR, SD, and DP.[1]

Two systematic reviews reported on lenvatinib.[1,26] One systematic review that included 1 phase II study on lenvatinib reported on PFS, OR, DP, SD.[1] The other systematic review included 2 phase II trials on lenvatinib and reported on PFS.[26]

Three systematic reviews reported on sorafenib.[1,26,27] One systematic review included 8 studies (3 phase II, 4 retrospective, and 1 observational) on the sorafenib and reported

on PFS, OR, DP, and SD.[1] The second systematic review included 9 studies (4 phase II, 4 retrospective, and 1 prospective) on sorafenib and reported on PFS, PR, and SD.[26] The third systematic review included 8 studies (3 phase II, 4 retrospective, and 1 prospective) on sorafenib and reported on PFS, PR, and SD.[27]

For patients with MTC, PFS ranged from 9.0 months (95% CI, 1.50 to 16.50) for lenvatinib to 16.50 months (95% CI, 2.45 to 30.55) for sunitinib.[1] PFS is defined as "the time from randomization until objective tumor progression or death" [46]

The proportion of patients with MTC achieving OR ranged from 44.07% (95% CI, 30.85 to 57.29) for lenvatinib to 71.43% (95% CI, 37.78 to 105.07) for sorafenib or sunitinib.[1] OR is a culmination of CR and PR. CR is defined as "disappearance of all target lesions." PR is defined as "at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD."[47] PR was reported for sorafenib only and ranged from 21% (95% CI, 9 to 33; I^2 = 63%)[27] to 23% (95% CI, 1 to 45; I^2 = 0.00%; P = 0.61)[26] between the 2 systematic reviews that reported this outcome.

Overall DP ranged from 11.86% (95% CI, 2.85 to 20.87) for lenvatinib to 60.00% (95% CI, 42.99 to 77.01) for pazopanib.[1] PD is defined as "at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions."[47]

SD ranged from 14.29% (95% CI, 1.56 to 27.01)[1] for pazopanib to 77.0% (95% CI, 45 to 100; I^2 = 48.9%; P = 0.42)[26] for sorafenib.SD is defined as "neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started."[47]

Harms Results

The safety of cabozantinib, selpercatinib, sunitinib, pazopanib, sorafenib, or lenvatinib are summarized as follows. Data on the safety of cabozantinib and selpercatinib are based on the product labels and HTA reports[10,33-38,44,45] (refer to Appendix 4). Data on the safety of sunitinib, pazopanib, sorafenib or lenvatinib were gathered from the 3 systematic reviews and meta-analysis.[1,26,27] Appendix 8 present the safety results on these 4 TKIs. The Health Canada product monographs (for indications other than MTC) for these drugs were also reviewed for any additional safety information. Given that these systematic reviews and meta-analyses also included cabozantinib, any relevant safety data on the drug were also gathered.

Cabozantinib

Deterioration in quality of life was observed in the cabozantinib group after 12 weeks of treatment compared with placebo owing to an increase in the incidence and severity of symptoms, particularly gastrointestinal symptoms. More than 75% of the patient population needed a dose reduction due to AEs. Therefore, some of the HTA bodies highlighted that the optimal dosage of cabozantinib has yet to be determined. Drug discontinuation due to AEs was twice as high in the cabozantinib group as in the placebo group.[29,33,35,37]

Selpercatinib

No comparative safety data were available. Information on treatment-emergent AEs, serious AEs (SAEs), death, drug discontinuation, and dose interruption and reduction is presented in Appendix 4 and based on Health Canada's product monograph. This safety data are inclusive of all the subgroups in the LIBERTTO-001 trial; that is, people with advanced solid tumours; with *RET* activations, including *RET* fusion-positive non–small cell lung cancer; *RET*-mutant MTC; and *RET* fusion-positive advanced TC.[10]

Pralsetinib

No comparative safety data were available. Information on treatment-emergent AEs, SAEs, death, drug discontinuation, and dose interruption and reduction are presented in Appendix 4 and based on the FDA's prescribing information. This safety data are inclusive of all the subgroups of *RET*-altered TC in the ARROW trial; that is, patients with *RET*-mutant MTC and *RET* fusion-positive TC.[11]

Systematic Reviews: Cabozantinib, Sunitinib, Pazopanib, Lenvatinib, and Sorafenib

One systematic review reported on drug discontinuation and grade 3 or 4 AEs on cabozantinib.[1]

None of the systematic reviews reported on safety outcomes for sunitinib.

One systematic review reported on drug discontinuation and grade 3 or 4 AEs for pazopanib.[1]

Two systematic reviews reported on lenvatinib.[1,26] One reported on drug discontinuation and grade 3 or 4 AEs.[1] The other reported on drug discontinuation, grade 3 or 4 adverse events, and AEs of any grade.[26]

Three systematic reviews reported on sorafenib.[1,26,27] One reported on drug discontinuation and grade 3 or 4 AEs.[1] The second reported on drug discontinuation, grade 3 or 4 AEs, and AEs of any grade.[26] The third reported on drug discontinuation, grade 3 or 4 AEs, and AEs of any grade.[27]

Drug discontinuation ranged from 16% (95% CI, 6 to 26; $I^2 = 0.00\%$; $P = 0.62$)[26] for sorafenib to 77.14% (95% CI, 62.29 to 92.00)[1] for pazopanib. Combined grade 3 or more AEs ranged from 14.29% (95% CI, 1.56 to 27.01) in pazopanib to 66.72% (95% CI, 60.75 to 72.68; $I^2 = 0.00\%$; $P = 0.505$) in cabozantinib.[1]

Appendix 9 presents information on treatment-emergent AEs and SAEs from Health Canada's product monographs for sorafenib, sunitinib, lenvatinib, and pazopanib across any Health Canada–approved indication.

Limitations

The overall evidence presented in this report was drawn from HTA reports, product labels, and systematic reviews. This poses a challenge in comparing the drugs and their outcomes. The comparison is further challenged by the significant heterogeneity in the included studies, which also limits the reliability of the findings. The heterogeneity in the included studies was attributed to differences in the definition of PD and the time lapse between the diagnosis of DP, as well as differences in patient ethnicity, treatment duration, and follow-up.[1,26,27] There was also overlap of primary studies (for sorafenib and levantinib) across the 3 systematic reviews, resulting in the same outcomes being reported 2 or more times.

For some drugs, the number of primary studies was small. One study noted that a meta-analysis could not be performed on cabozantinib and levantinib due to the small number of studies.[26] Further head-to-head comparison between the different drugs was not available in any primary studies (randomized controlled trials).[1,26,27] Additionally, many of the primary studies in all 3 systematic reviews were not placebo controlled. One systematic review noted that some randomized controlled trials were treated as observational studies, and only the data from the treatment arm were included in the main analyses;[1] thus, it was difficult to compare efficacy or harms. Key methodological limitations of the included reviews were assessed using the AMSTAR 2 tool and are presented in Appendix 2.

It is also unclear how many of the primary studies included in the systematic reviews were conducted in Canada; as such, the generalizability of the results to the Canadian setting is unknown. The efficacy data on pralsetinib are only based on the FDA's prescribing information. Furthermore, efficacy data on cabozantinib and selpercatinib for use in patients with MTC were drawn from HTA assessments conducted in the UK, Scotland, and France. The applicability of the reimbursement recommendation in the Canadian context is not known.

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Appendix 1: Regulatory Status and HTA Recommendations

Note that this appendix has not been copy-edited.

Table 3: Regulatory Status and HTA Recommendations

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
Vandetanib			
Monotherapy for the treatment of symptomatic or progressive MTC in adult patients with unresectable locally advanced or metastatic disease	• FDA: For the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. • EMA: for the treatment of adults, children and adolescents aged 5 years and older, with aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. • TGA: indicated for the treatment of patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.	CADTH: pERC recommends reimbursement of vandetanib conditional on the cost-effectiveness being improved to acceptable level. Funding should be for the treatment of patients who have symptomatic and/pr progressive MTC with unresectable locally advanced or metastatic disease and with a good performance status. Treatment should continue until disease progression or unacceptable toxicity.	"There is modest net clinical benefit of vandetanib based on a clinically meaningful improvement in PFS compared with placebo, and a need for more effective treatment options. The committee noted uncertainty in OC and quality of life benefits, and manageable but not insignificant toxicities. pERC also concluded that vandetanib partially aligned with patient values in that it offers an improvement in PFS and it provides patients with a treatment option in addition to best supportive care, but with a risk of toxicities."
Cabozantinib[c]			

• For the treatment of advanced RCC:
  ○ In treatment-naïve adults with intermediate or poor risk.
  ○ In adult patients who have received prior VEGF targeted therapy.
  ○ Cabozantinib, in combination with nivolumab, is indicated for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC.
	• FDA: For the treatment of patients with progressive, metastatic MTC.
	• EMA: For the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. For patients in whom *RET* mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.
		NICE: Cabozantinib is recommended, within its marketing authorisation, as an option for treating progressive medullary thyroid cancer in adults with unresectable locally advanced or metastatic disease, only if the company provides cabozantinib with the discount agreed in the patient access scheme.	"Clinical trial evidence suggests that cabozantinib is effective in delaying disease progression compared with best supportive care but may not prolong survival. Without reliable comparative data, it was considered that cabozantinib and vandetanib are likely to be similarly effective."

		SMC: Cabozantinib is not recommended for use within NHS Scotland.	"In one pivotal, phase III study, cabozantinib was associated with a significant advantage in progression-free survival over placebo. However, the difference between

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
• For the treatment of patients with HCC who have been previously treated with sorafenib. • For the treatment of adult patients with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.			cabozantinib and placebo did not reach statistical significance in the subgroup of patients with Rearranged during Transfection (*RET*) negative tumours. The summary of product characteristics therefore notes that for patients in whom *RET* mutation status is unknown or is negative, a possible lower benefit should be taken into account before individual treatment decision."
		HAS: Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.	"The actual benefit[d] of cabozantinib is substantial. Like vandetanib, cabozantinib provides minor clinical added valueb (CAV IV) in the treatment of adults with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC). Role of the medicinal product in the therapeutic strategy: Cabozantinib is an alternative to vandetanib in the first-line treatment of patients with progressive advanced or metastatic MTC."
Selpercatinib[c,e]			
• For the treatment of metastatic *RET* fusion-positive NSCLC in adult patients. • For the treatment of *RET*-mutant MTC in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease. • For the treatment of *RET* fusion-positive DTC in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive	• FDA: For the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy • EMA: As monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.	NICE: Selpercatinib is recommended for use within the Cancer Drugs Fund, as an option for treating advanced *RET*-mutant medullary thyroid cancer in people 12 years and older who need systemic therapy after cabozantinib or vandetanib. It is recommended only if the conditions in the managed access agreement are followed	"People with advanced *RET*-mutant medullary thyroid cancer are usually offered a partial or full thyroidectomy, followed by cabozantinib. Clinical trial evidence for selpercatinib is highly uncertain because it is based on an ongoing single-arm trial and not all subpopulations represent NHS practice. The results comparing selpercatinib indirectly with best supportive care are also highly uncertain.

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
iodine therapy) following prior treatment with sorafenib and/or lenvatinib. **Notes:** • Indicated as monotherapy for the treatment • Treatment should only be initiated following confirmation of a *RET* gene fusion or mutation using a validated test			Data from the trial and NHS practice would also help address the uncertainty about its clinical effectiveness. Selpercatinib is therefore recommended for use in the Cancer Drugs Fund so that more data can be collected."
		SMC: Selpercatinib is accepted for use within NHS Scotland on an interim basis subject to ongoing evaluation and future reassessment.	"In a phase I/II study, in previously treated patients with *RET*-mutant MTC, selpercatinib was associated with an objective response rate of 69%. This advice applies only in the context of an approved NHS Scotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower."
		HAS: Favourable opinion for reimbursement as monotherapy in the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib. Maintenance of this opinion is conditional on the re-evaluation of this medicinal product within a maximum period of 3 years on the basis of: • comparative data for selpercatinib versus the standard of care for patients receiving second or later-line therapy, as well as the results of the phase 3 study in first-line	"Selpercatinib, as monotherapy provides no clinical added value (CAV V)[f] in the care pathway for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib. This is considering the not very robust quality of research evidence for the efficacy of selpercatinib based on data from a non-comparative phase 1/2 study (LIBRETTO-001), for which inclusions are ongoing; the absence of external comparison at least with a historic cohort; uncertainties with respect to maintenance of the efficacy of the objective response rates observed, with a short follow-

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
		treatment (LIB*RET*TO-531, results expected by February 2025 at the latest), in *RET*-mutant MTC, and data from the registry of patients treated in France with selpercatinib with *RET*-mutant MTC.	up period; the prognostic value of *RET* alteration, inadequately determined in the absence of comparative data, the very limited number of data in children in MTC. Despite the low level of evidence of the data, taking into account the substantial medical need (supported by patient associations and experts, in particular) and pending new efficacy and safety data, selpercatinib, as monotherapy is considered a treatment option for the management of advanced *RET*-mutant medullary thyroid cancer (MTC) following prior treatment with cabozantinib and/or vandetanib. The Committee highlights the fact that only one 17-year-old patient was treated in the study. It is necessary to highlight that in a context in which no comparative data is available to guarantee the solidity of the conclusion with respect to the effect of treatment with selpercatinib, the introduction of this medicinal product into the treatment strategy is accompanied by a higher risk than for medicinal products for which the efficacy is based on a comparison conducted with control of the risk of wrongly concluding that the treatment is effective (two-tailed alpha risk conventionally accepted to be 5%)."
Pralsetinib			
• For the treatment of adult patients with *RET*-fusion-positive locally advanced	• FDA: For the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic	NA	

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
unresectable or metastatic NSCLC.	*RET*-mutant MTC who require systemic therapy.		
Sunitinib			
• For the treatment of GIST after failure of imatinib mesylate treatment due to resistance or intolerance. • For the treatment of mRCC of clear cell histology • For the treatment of patients with unresectable locally advanced or metastatic, well differentiated pancreatic NET, whose disease is progressive.	NA		
Pazopanib			
• For the treatment of patients with mRCC (clear cell) as first-line systemic therapy or as second-line systemic therapy after treatment with cytokines for metastatic disease. • For the treatment of adult patients with selective subtypes of advanced STS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.	NA		
Sorafenib			
• For the treatment of patients with unresectable **HCC**. There are limited safety data available for Child-Pugh Class B patients • For the treatment of locally advanced / metastatic **RCC** in patients who failed or are intolerant to prior systemic therapy.	NA		

Health Canada Approved Indication (any)	MTC Indication if approved in jurisdiction other than Canada[a]	HTA Recommendation for MTC indication only[b]	Clinical Rationale for Recommendation
• For the treatment of patients with locally advanced or metastatic, progressive **DTC** refractory to radioactive iodine.			
Lenvatinib			
• For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory **DTC**. • In combination with everolimus for the treatment of patients with advanced **RCC** following one prior vascular endothelial growth factor (VEGF)- targeted therapy. • For the first-line treatment of adult patients with unresectable **HCC**. Efficacy and safety data for Child-Pugh Class B and Class C are not available. • In combination with pembrolizumab, for the treatment of adult patients with advanced **endometrial carcinoma that is not MSI-H or dMMR**, who have disease progression following prior platinum-based systemic therapy and are not candidates for curative surgery or radiation. *[Marketing authorization issues with conditions, pending the results of trials to verify its clinical benefit]*	NA		

AE = Adverse Events; CADTH = Canadian Agency for Drugs and Technologies in Health; CDR = Common Drug Review; DCR = disease control rate; dMMR = mismatch repair deficient; DOR = duration of response; DTC = differentiated thyroid cancer; EMA = European Medicines Agency; FDA = Food And Drug Administration, US; G3AEs = grade ≥3 AEs; GIST = Gastrointestinal stromal tumour; HAS = Haute Autorité de santé; HCC = Hepatocellular carcinoma; HTA = Health Technology Assessments; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; mRCC = Metastatic Renal Cell Carcinoma; MSI-H = microsatellite instability high; MTC = Medullary thyroid carcinoma; NA = not applicable; NET = neuroendocrine tumours; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; NSCLC = non-small sell lung cancer; ORR = objective response rate; OS = over- all survival; PBAC = Pharmaceutical Benefits Advisory Committee; pCODR = pan-Canadian Oncology Drug Review; pERC = pCODR Expert Review Committee; PFS = progression-free survival; RCC = Renal cell carcinoma; STS = Soft Tissue Sarcoma; TGA = Therapeutic Goods Administration, Australia; PHARMAC = Pharmaceutical Management Agency; *RET* = Rearranged during Transfection; SAE = Serious Adverse Events; SMC = Scottish Medicines Consortium; SR = systematic review; VEGF = vascular endothelial growth factor.

[a] The following regulatory bodies were searched for the information: Health Canada, FDA (US), EMA (Europe), TGA (Australia), MedSafe (New Zealand)

[b] Following HTA agencies were searched for the information CADTH, INESSS, NICE, SMC, HAS, IQWiG, PBAC and PHARMAC. If the drug was assessed by CADTH for MTC indication, then only the reimbursement recommendation from CADTH is presented. In instances when CADTH has not assessed the drug for MTC, reimbursement recommendation from the other HTA agencies (for MTC) were presented.

[c] Given that documents related to IQWiG's assessment of cabozantinib and selpercatinib are only available in German language, and this CADTH review is limited to English language, further details IQWiG's assessment is unavailable.

[d] The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

[e] Selpercatinib is currently under review at CADTH.

[f] The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".

Sources: Information based on product labels and HTA reports[3,5,6,9-12,14,16,20,22,28-31,33-40,44,45,48,49]

Appendix 2: Strengths and Limitation of Systematic Reviews and Meta-Analysis

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitation of Systematic Reviews and Meta-Analysis Using AMSTAR[25]

Strengths	Limitation
Efstathiadou et al. (2021)	
• The research question and inclusion criteria for the review included components of population, intervention, comparators and outcomes. They were relevant to the current report. No major intervention or comparators were excluded from eligibility. • The systematic review was registered in PROSPERO. • Clinical trials, observational, prospective, and retrospective studies were included. IT was noted that all studies were included to avoid a systemic selection bias. • A list of excluded studies and the reason for exclusion was provided. • A comprehensive literature search across multiple databases was used to identify eligible studies. Key word and search strategies were reported. • Four groups of two reviewers each independently performed data extraction • Quality assessment of the studies was performed • It was noted that there were no funding sources to declare. • The method for statistical combination of results were explained, and statistical tools used were identified. Heterogeneity was calculated using Cochrane's Qx^2 test and I^2 statistic. The DerSimonian and Laird method was used for the estimation of summarized effect size in each subanalysis. • Conflict of interest was declared	• It was unclear if the review methods deviated from the planned protocol • It was unclear if study selection was done in duplicates • A baseline characteristics of individual study participants was not reported. • Risk of bias assessment of the included studies was not performed, and neither was its potential impact assessed or discussed in interpreting the results.
Oba et al. (2020)	
• The research question and inclusion criteria for the review included components of population, intervention, comparators and outcomes. They were relevant to the current report. No major intervention or comparators were excluded from eligibility • Clinical trials, observational, prospective, and retrospective studies were included.	• It was unclear if the review methods were established a priori • A rationale for inclusion of the types of studies were not provided • It was unclear if data extraction was done in duplicates • Funding sources were not declared. • Risk of bias assessment of the included studies was not performed, and neither was its potential impact assessed or discussed in interpreting the results.

Strengths	Limitation
• A comprehensive literature search across multiple databases was used to identify eligible studies. Key word and search strategies were reported. • A list of excluded studies and the reason for exclusion was provided. • Two reviewers independently determined the eligibility of studies for inclusion. • Some characteristics of the included studies such as population (baseline median age, and ECOG status) was reported. • Egger's test was carried out to evaluate the publication bias. • The method for statistical combination of results were explained, and statistical tools used were identified. Heterogeneity was calculated using I^2 statistic. • Authors declared no conflicts of interest	
Vuong et al. (2019)	
• The research question and inclusion criteria for the review included components of population, intervention, comparators and outcomes. They were relevant to the current report. No major intervention or comparators were excluded from eligibility • Clinical trials, observational, prospective, and retrospective studies were included. • A comprehensive literature search across multiple databases was used to identify eligible studies. Key word and search strategies were reported. • A list of excluded studies and the reason for exclusion was provided. • Two reviewers independently determined the eligibility of studies for inclusion • Two reviewers independently performed data extraction • Some characteristics of the included studies such as population (baseline median age, and ECOG status, *RET* mutation and previous treatment)) was reported. • Egger's test was carried out and funnel plot was used to evaluate the publication bias. • The method for statistical combination of results were explained, and statistical tools used were identified. Heterogeneity was calculated using I^2 statistic. • Authors declared no conflicts of interest	• It was unclear if the review methods were established a priori • A rationale for inclusion of the types of studies were not provided • Funding sources were not declared. • Risk of bias assessment of the included studies was not performed, and neither was its potential impact assessed or discussed in interpreting the results.

Appendix 3: Mechanisms of Action and Approved Doses

Table 5: Summary of Drug Characteristics — Mechanisms of Action, Approved Dose, Formulation, and Dosage Form

Drug	Mechanism of Action (Target Molecules)[a]	Approved Dose for MTC	Health Canada approved dose (only for indication other than MTC, and only if not indicated in Canada for MTC)	Formulation and Dosage form available in Canada
Vandetanib	Vandetanib is a potent and selective inhibitor of VEGFR2, KDR, EGFR, and *RET* receptor tyrosine kinases. At sub-micromolar concentrations vandetanib also inhibits VEGFR-3 (Flt-4) and VEGFR-1 (Flt-1).	Health Canada 300mg OD	NA	Tablets 100mg, 300 mg Oral
Cabozantinib	Cabozantinib has activity against MET (hepatocyte growth factor receptor protein, VEGFR2, the glial cell-line derived neurotrophic factor receptor, GAS6 receptor (AXL), stem cell factor receptor (KIT), FLT3, and others. In cell culture and animal models, cabozantinib prevented phosphorylation of its target kinases, reduced cell proliferation, and limited angiogenesis, tumor invasiveness, and metastasis of multiple cancer cell lines.	FDA and EMA 140 mg OD (capsules)	RCC, HCC, DTC: Monotherapy: 60mg OD, first dose reduction to 40mg OD, second dose reduction to 20 mg OD In Combination with nivolumab: 40mg OD, first dose reduction to 20mg OD, second dose reduction to 20 mg every other day.	Tablets, 20 mg, 40 mg, 60 mg Oral
Selpercatinib	Selpercatinib has shown to inhibit *RET* receptor tyrosine kinase, VEGFR3 (FLT4) and VEGFR1 (FLT1), FGFR1, 2 and 3. In *RET* enzyme assays, selpercatinib inhibits the kinase activity of wild type *RET* and multiple mutated forms of *RET* (*RET*-V804L, *RET*-V804M, *RET*-A883F, *RET*-S904F, and *RET*-M918T)	Health Canada < 50 kg: 120 mg BID ≥50Kg: 160 mg BID	NA	Capsules 40 mg and 80 mg Oral

Drug	Mechanism of Action (Target Molecules)[a]	Approved Dose for MTC	Health Canada approved dose (only for indication other than MTC, and only if not indicated in Canada for MTC)	Formulation and Dosage form available in Canada
Pralsetinib	Pralsetinib is an inhibitor of wild-type *RET* and oncogenic *RET* fusions (CCDC6-*RET*) and mutations (*RET* V804L, *RET* V804M and *RET* M918T). In purified enzyme assays, pralsetinib inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, and FGFR1.	FDA: 400 mg OD	NSCLC: 400mg OD	Capsules 100 mg Oral
Sunitinib	Sunitinib has shown to be a potent inhibitor of PDGFRα and PDGFRβ, VEGFR1, VEGFR2 and VEGFR3, KIT, FLT3, colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor. Sunitinib effectively blocked phosphorylation of the *RET* V804M mutant.	NA	GIST: 50-mg OD (4 weeks on treatment followed by 2 weeks off) mRCC: 50-mg OD (4 weeks on treatment followed by 2 weeks off) pancreatic NET: 37.5 mg OD (no scheduled off-treatment period).	Capsule 12.5 mg, 25 mg, 37.5 mg, 50 mg Oral
Pazopanib	Pazopanib is also a potent inhibitor of VEGFR1, VEGFR2 and VEGFR3, PDGFRα and PDGFRβ, and c-KIT.	NA	mRCC: 800 mg OD STS: 800 mg OD	Tablets 200 mg Oral
Sorafenib	Sorafenib has demonstrated activity against multiple intracellular (c-CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, *RET*, *RET*-PTC, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Sorafenib effectively blocked phosphorylation of the *RET* V804M mutant.	NA	HCC: 400 mg BID RCC: 400 mg BID DTC: 400 mg BID	Tablet 200 mg Oral
Lenvatinib	Lenvatinib selectively inhibit the kinase activities of VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), as well as FGF receptors FGFR1, 2, 3, and 4, PDGFRα, KIT and *RET*.	NA	DTC: 24 mg OD RCC: 18 mg OD *in combination with 5 mg everolimus*. HCC: • < 60 kg: 8 mg OD • ≥ 60 kg: 12 mg OD	Capsules 4mg and 10mg Oral

Drug	Mechanism of Action (Target Molecules)[a]	Approved Dose for MTC	Health Canada approved dose (only for indication other than MTC, and only if not indicated in Canada for MTC)	Formulation and Dosage form available in Canada
			Endometrial carcinoma: 20 mg OD *in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks*	

BID = bis in die (twice a day); DTC = Differentiated thyroid cancer; EGFR = epidermal growth factor receptor; FGF = fibroblast growth factor; FLT = Fms-like tyrosine kinase; GIST = Gastrointestinal stromal tumor; HCC = Hepatocellular carcinoma; mRCC = Metastatic Renal Cell Carcinoma; MTC = Medullary Thyroid Cancer; NET = neuroendocrine tumors; NA = not applicable; OD = once daily; PDGFR = platelet-derived growth factor receptors; RCC = Renal cell carcinoma; *RET* = rearranged during transfection; STS = Soft Tissue Sarcoma; VEGFR = vascular endothelial growth factor receptors

[a] Vendetanib, cabozantinib, sunitinib, sorafenib, pazopanib, lenvatinib, and selpercatinib, classified as tyrosine kinase inhibitors (TKI), are small molecules that inhibits multiple receptor tyrosine kinases (RTK) implicated in tumour growth and angiogenesis, pathologic bone remodeling, drug resistance, and/or metastatic progression of cancer. *In-vitro* and *in-vivo* studies have shown their activity on several important kinases that are responsible for tumor progression in MTC.

Sources: Information based on product labels. [6,10,14,16,20,28-31,40,48,50] [11,12]

Appendix 4: Study Characteristics and Results From Pivotal Studies

Note that this appendix has not been copy-edited.

Table 6: Study Characteristics and Results From Pivotal Studies Used For Regulatory Approval and Reimbursement Reviews

Drug Study design	Population	Results	Notes
Cabozantinib Phase III Multicenter, International, Double blind, Placebo-controlled RCT (EXAM)	N = 330 • Cabozantinib 140 mg OD (capsules) without food, until disease progression determined by the treating physician or until intolerable toxicity (n = 219) • Placebo (n = 111) Patient Characteristics Sex • Male = 67% • Female = 33% Age • <65 years old = 77% • ≥ 65 years = 23% Median age = 55 years Race • White = 89% *RET* status • positive = 48.1% • Negative = 12.4% • Not known = 39.3% Disease state: actively progressive disease within 14 months prior to study entry confirmed by an Independent Radiology Review Committee (IRRC) masked to treatment assignment (89%) or the treating physician (11%). • Baseline ECOG (0) = 54% • Metastases in at least two localizations = 87% Prior Treatment:	**Efficacy** Median PFS • Cabozantinib = 11.2 months • Placebo = 4 months Absolute gain of 7.2 months in favour of cabozantinib (HR = 0.28, 95% CI, 0.19; 0.40; P < 0.0001); with a median trial follow-up of 13.9 months No difference in PFS between cabozantinib and placebo in patients with a negative *RET* status. median OS • Cabozantinib = 26.6 months • Placebo = 21.1 months Not statistically significant (HR 0.85; 95% CI, 0.64 to 1.12), with a median trial follow-up of 52 months. QoL • Deterioration of QoL in cabozantinib group after 12 weeks of treatment compared with placebo owing to an increase in the incidence and severity of symptoms, particularly gastrointestinal. **Safety** Dose reduction • Only 23.8% kept to the recommended dosage of 140 mg/day Drug discontinuation due to AEs • Cabozantinib = 16.4% of patients • Placebo = 8.3% of patients Most common SAEs:	No cross-over allowed at the time of progression. Possibility of lower benefit must be considered *in* patients in whom *RET* mutation status is not known or negative. HAS noted that no conclusions could be drawn about the efficacy of cabozantinib in patients previously treated with vandetanib, as the number such patient in the study was low (34/330; approximately 10%). NICE's assessment group concluded that cabozantinib and vandetanib are likely to be similar based on an indirect treatment comparison (NMA). The NMA showed that in terms of PFS the two treatments were broadly similar. Of note, overall survival was not included in this analysis. Lack of robust comparative data was noted. Clinical experts consulted were of the opinion that both drugs have similar effectiveness in terms of delaying progression and controlling symptoms, but there was no evidence of prolonging survival; and that the choice between the two was related more to their differing toxicity profiles

Drug Study design	Population	Results	Notes
	• undergone a thyroidectomy = 92% • Two or more prior systemic therapies = 25% • Prior treatment with a TKI = 21%	• pneumonia, mucositis, hypocalcaemia, dysphagia, dehydration, pulmonary embolism and hypertension. Most common AEs (of any grade reported in at least 20% of patients): • diarrhoea, palmar-plantar erythrodysaesthesia syndrome, arterial hypertension, stomatitis, constipation, vomiting and mucositis.	than their relative effectiveness. Optimal dosage of cabozantinib has yet to be determined. Over three quarters of the patient population needed a dose reduction due to AEs. A recently published phase IV, randomized, double-blind, non-inferiority study comparing cabozantinib140mg/day capsules with cabozantinib 60mg/day tablets concludes that "progression-free survival (PFS) non-inferiority of the cabozantinib 60 mg/day tablet versus 140 mg/day capsules was not met. The 60 mg/day tablet had the same objective response rate (ORR) and lower rates of adverse events (AEs)" (pg. 1).

Selpercatinib
 	
ongoing single-arm, open-label, multicentre, multi-cohort phase I/II clinical trial (LIBRETTO-001)[a]
	Two subgroups
	• Previously treated with vandetanib or cabozantinib or both (n=55)
	  ○ Treated with vandetanib (76.4%)
	  ○ Treated with cabozantinib (67.3%)
	  ○ Mean Age = 57 (17-84) years (One pediatric patient (17 years of age))
	  ○ Sex: male 36 (66%); female 19 (34%)
	  ○ Race: White (89%), Hispanic/Latino (7%), Black (1.8%).
	  ○ ECOG performance status: 0-1 (95%) or 2 (5%),
	  ○ Patients with metastatic disease: 98%
	  ○ Patients received a median of 2 prior systemic therapies: range 1-8
		Efficacy
		Previously treated with vandetanib or cabozantinib or both (n = 55)
		
		ORR[b]: 69% (95% CI, 55-81)
		• CR: 9.1%
		• PR: 60%
		
		DOR[b]
		• Median duration of follow-up 14.1 months
		• Patients with response: 38
		• DOR events: 6
		• Median DOR: NE (95%CI, 19.1 to NE)
		• KM estimate at 12 months: 86%
		
		PFS[b]
		• Median duration of follow-up: 16.7 months
		• Median PFS: NE (24.4 to NE)
		• KM estimate at 12 months: 82%
		
		Vandetanib and cabozantinib treatment-naïve patients (n=88)
			Data cut off 16 December 2019
			
			SMC note the availability of an updated analysis at data cut-off 30 March 2020 of the primary analysis set. There was no further ORR but one patient previously assessed as having a PR was upgraded to CR. Median duration of response, medial PFS was NE. Median overall survival was 33.2 months (with 13 deaths).
			
			The company conducted additional analysis, the results of which were noted to be uncertain or highly uncertain. NICE concluded that the company's matching-adjusted indirect treatment comparisons

Drug Study design	Population	Results	Notes
	○ *RET* mutation status detection method: NGS (82%), PCR (16%), unknown test (2%). Excluded patients with synonymous, frameshift, or nonsense *RET* mutations • Vandetanib and cabozantinib treatment-naïve patients (n=88) ○ Mean Age = 58 (15-82) years ○ Sex: male 58 (66%); female 30 (34%) ○ Race: White (86%), Asian (4.5%), Hispanic/Latino (2.3%). ○ ECOG performance status: 0-1 (97%) or 2 (3%), ○ Patients with metastatic disease: 100% ○ Patients receiving 1-2 prior systemic therapies: 18% (kinase inhibitors (8%), chemotherapy (3.4%), anti-PD1/PD-L1 therapy (2.3%), and radioactive iodine (1.1%) ○ *RET* mutation status detection method: NGS (77.3%), PCR (18.2%), unknown test (4.5%). Selpercatinib 160mg BD until unacceptable toxicity of disease progression Disease state: patients with *RET*-mutant MTC.	ORR[b]: 73% (95% CI, 62-82) • CR[a]: 11% • PR[a]: 61% **Safety** (n = 702, all subgroups in LIBERTTO-001; people with advanced solid tumours, with *RET* activations) • TEAEs (of any grade reported in at least 25% of patient in order of decreasing frequency: increased AST, increased ALT, lymphocyte count decreased, glucose increased, leukocytes decreased, albumin decreased, calcium decreased, dry mouth, creatinine increased, diarrhea, alkaline phosphatase increased, hypertension, platelets decreased, total cholesterol increased, fatigue, rash, sodium decreased and constipation. • SAEs: 33% of patients who received selpercatinib • SAEs (in ≥2% of patients): pneumonia and hemorrhage • Deaths due to an AE: 3% of patients • Deaths (events that occurred in >1 patient):sepsis (n=3), cardiac arrest (n=3), respiratory failure (n=3), and hemorrhage (n=3). • Permanent discontinuation due to an AE: 5% of patients who received selpercatinib • AE resulting in permanent discontinuation: increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%). • Dosage interruptions due to an AE: 42% of patients who received selpercatinib • AE requiring dosage interruption (>2% of patients): ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.	(MAIC) between selpercatinib (LIBERTTO-001) with cabozantinib (EXAM) and placebo (a proxy for best supportive care) for *RET*-mutant MTC contained multiple sources of uncertainty, and the results were therefore uncertain. NICE also noted that the company's extrapolation of PFS and OS in *RET*-mutant MTC was highly uncertain.

Drug Study design	Population	Results	Notes
		• Dose reductions due to an AE: 31% of patients who received selpercatinib • AE requiring dosage reductions (in >2% of patients): ALT increased, AST increased, QT prolongation, and fatigue.	
Pralsetinib Non-randomized, open-label, multicentre, multi-cohort phase I/II clinical trial (ARROW)[c]	Two subgroups • Previously treated with vandetanib or cabozantinib or both (n=55) ○ Median Age = 59 years (range: 25 to 83); ○ Sex = Male (69%) ○ Race = White (78%), Asian (5%), Hispanic/Latino (5%) ○ ECOG performance status: 0-1 (95%) or 2 (5%), ○ History of CNS metastases = 7% ○ Patients received a median of 2 prior therapies (range 1-7). ○ *RET* mutation status detection method: 73% using NGS [55% tumor sample, 18% plasma], 26% using PCR sequencing, and 2% other. ○ *RET* Mutation type: M918T [d] (37), Cysteine Rich Domain[e] (11), V804M or V804L (2) and Other[f](5) • Vandetanib and cabozantinib treatment-naïve patients (n=29) ○ Median Age = 61 years (range: 19 to 81); ○ Sex = Male (72%) ○ Race = White (76%), Asian (17%), Hispanic/Latino (3.4%) ○ ECOG performance status: 0-1 (100%), ○ Metastatic disease = 97% ○ History of CNS metastases = 14% ○ Received up to 3 lines of prior systemic therapy = 28% (10% PD-1/PD-L1 inhibitors, 10% radioactive	**Efficacy** Previously Treated with Cabozantinib or Vandetanib (n = 55) • ORR[g] (95% CI): 60 (46, 73) ○ CR = 1.8% ○ PR = 58% • DOR (n=33) ○ Median in months (95% CI) = NR (15.1, NE) • Efficacy Parameters (n = 55) ○ Patients with DOR ≥ 6 months[h] = 79% Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC (n = 29) • ORR[g] (95% CI): 66 (46, 82) ○ CR = 10% ○ PR = 55% • DOR (n=19) ○ Median in months (95% CI) = NR (NE, NE) ○ Patients with DOR ≥ 6 months[h] = 84% **Safety** • SAE = 39%. • SAE in ≥ 2% of patients: pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. • Fatal AE = 2.2% of patients; fatal AE that occurred in > 1 patient included pneumonia (n=2). • Permanent discontinuation due to an AE = 9% • Permanent discontinuation due to AE in > 1 patient: fatigue, pneumonia and anemia. • Dosage interruptions due to an AE = 67% • Dosage interruption due to in ≥ 2% of patients: neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased	NA

Drug Study design	Population	Results	Notes
	iodine, 3.4% kinase inhibitors) ○ *RET* mutation status detection method: 90% using NGS [52% tumor sample, 35% plasma, 3.4% blood], and 10% using PCR sequencing. ○ *RET* Mutation type: M918T [d] (15), Cysteine Rich Domain[e] (11), V804M or V804L (1) and Other[f](2) Disease state: patients with *RET*-mutant MTC. For Safety Assessment (*RET*-Altered Thyroid Cancer) (n=138) • Dose: monotherapy at 400 mg • Exposed for ≥6 months = 68% • Exposed for ≥1 year = 40% • Median age = 59 years (range: 18 to 83 years) • Sex: Female (36%), • Race = White (74%), Asian (17%), and Hispanic/Latino (6%)	blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting, pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope. • Dose reductions due to AE = 44% • Dosage reductions due to AE in ≥ 2% of patients = neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.	

AE = adverse events; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; Ci = confidence interval; CR = complete response; DOR = Duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HR = Hazard ratio; KM = Kaplan Meier; MTC = Medullary thyroid carcinoma; NE = non-evaluable/estimable; NGS = next generation sequencing; NMA = network meta-analysis; NR = not reached; OD = once daily; ORR = objective response rate; OS = overall survival; PD1 = Programmed death receptor 1; PFS = progression-free survival; PCR = polymerase chain reaction; PR = partial response; QoL = Quality of life; *RET* = Rearranged during Transfection; SAE = Serious Adverse Events; SD = stable disease; SR = systematic review; TEAEs = treatment emergent adverse events.

[a] LIBRETTO-001 was conducted on patients with *RET*-altered solid tumors, including *RET* fusion-positive non-small cell lung cancer; *RET*-mutant medullary thyroid cancer and *RET* fusion positive advanced thyroid cancer. Only information specific to *RET*-mutant medullary thyroid cancer is presented here.

[b] Determined by an independent review committee (IRC) according to RECIST v1.1 (for ORR).

[c] ARROW was conducted on patients with *RET* fusion NSCLC, *RET*-mutant MTC, *RET* fusion-positive thyroid cancer. Only information specific to *RET*-mutant medullary thyroid cancer is presented here

[d] Three patients (all in the prior cabozantinib and/or vandetanib group) also had a V804M/L mutation.

[e] Cysteine Rich Domain (including the following cysteine residues: 609, 611, 618, 620, 630, and/or 634)

[f] Other included: D898_E901del (1), E632_L633del (1), L790F (1), A883F (2), K666E (1), and R844W (1)

[g] Confirmed overall response rate assessed by blinded independent central review.

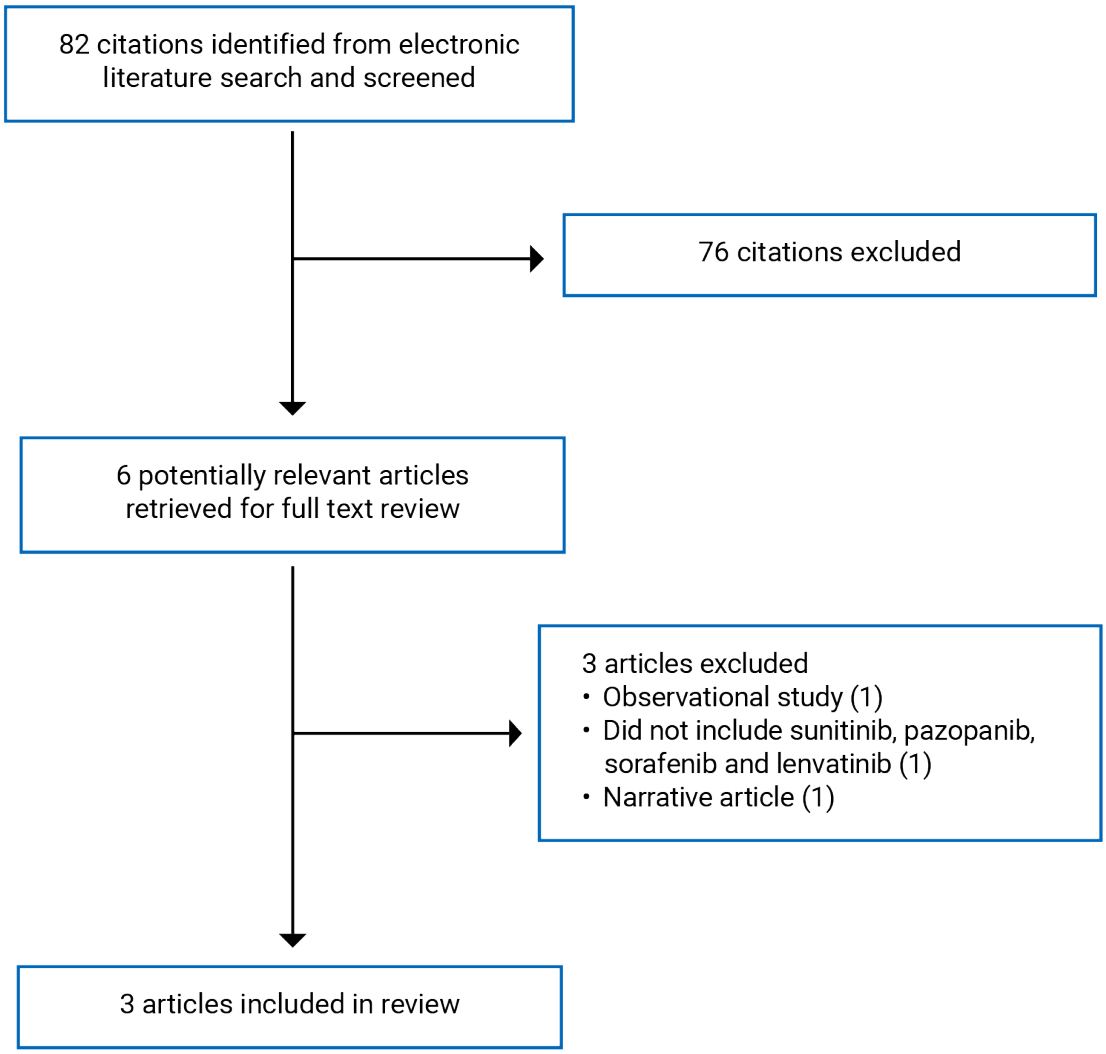
[h] Based on observed duration of response

Sources: HTA reports and product labels [10,33-38,44,45] [11,15]

Appendix 5: Included Studies

Note that this appendix has not been copy-edited.

Figure 2: Selection of Included Studies From The Literature Search



Appendix 6: Study Characteristics of Systematic Reviews and Meta-Analysis

Note that this appendix has not been copy-edited.

Table 7: Systematic Review and Meta-Analysis Study Characteristics

Studiy Citation, country, funding source	Study designs Numbers and types of primary studies included	Population	Interventions and Comparators	Outcomes (primary and secondary)
Efstathiadou et al. (2021) [1] Greece Funding sources: None declared	Study design: systematic review and meta-analysis Number of primary studies Included: 33 studies with 36 cohorts Number of studies relevant to this report: 15 Number of the different types of studies relevant to this report: Phase III (1), Phase II (7), Phase I (1), Observational (1), Retrospective (5)	Patients with MTC (progressive disease, or locally advanced or metastatic) N = 600 (only relevant studies)	**Eligible interventions:** Tyrosine Kinase Inhibitors (TKIs) Relevant Interventions: Cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib.	**Primary Outcomes** Efficacy: Objective response (OR) (complete + partial response) **Secondary Outcomes** Efficacy: Disease stability, disease progression (DP), median progression-free survival (PFS), Safety: Drug discontinuation due to AEs[a], G3AEs
Oba et al., 2020 [26] Japan Funding sources: None declared	Study design: systematic review and meta-analysis Number of primary studies Included: 34 Number of studies relevant to this report: 12 Number of the different types of studies relevant to this report: Phase III (1), Phase II (6), Retrospective (4), Prospective (1)	Patients >18 years of age thyroid cancer (ATC, DTC, MTC) N = 390 (MTC only)	**Eligible interventions:** Cabozantinib, lenvatinib, sorafenib and vandetanib. Relevant Interventions: Cabozantinib (140 mg OD[b]), lenvatinib (300 mg OD), sorafenib (400mg BD).	Efficacy: Response rate (CR, PR, SD), PFS and OS Safety: AEs
Vuong et al., 2019 [27] Japan Funding sources: None declared	Study design: systematic review and meta-analysis Number of primary studies Included: 8 Number of the different types of studies relevant to this report: Phase II (3), Retrospective (4), Prospective (1)	Patients with locally advanced or metastatic MTC N = 101	**Eligible interventions**: sorafenib (400mg BD).	Efficacy: CR, PR, SD Safety: SAEs

ATC = anaplastic thyroid cancer; CR = complete response, DTC = differentiated thyroid cancer; MTC = Medullary thyroid carcinoma; OR = objective response rate; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PR = partial response; *RET* = Rearranged during Transfection; SAE = Serious Adverse Events; SD = stable disease; SR = systematic review.

[a]Patients with drug interruption or dose reduction due to AEs were not included in the drug discontinuation outcome.

[b] capsule formulation

Source: Information based on systematic reviews[1,26,27]

Appendix 7: Efficacy Outcomes of Systematic Reviews and Meta-Analysis

Note that this appendix has not been copy-edited.

Table 8: Systematic Reviews and Meta-Analysis Study Findings — Efficacy Outcomes

Drug	Study Citation	Treatment response
Progression Free Survival (PFS)		
Cabozantenib	Efstathiadou et al. (2021)	11.20 months (95% CI 8.10-14.30)
	Oba et al. (2020)	11.20 months (HR 0.28; 95% CI, 0.19-0.40; P <0.01) [median]
Lenvatinib	Efstathiadou et al. (2021)	9.0 months (95% CI, 1.50-16.50)
	Oba et al. (2020)	9.0 months (95% CI, 7.0 – non evaluable)
Sorafenib	Efstathiadou et al. (2021)	12.39 months (95% CI, 8.35-16.44; I^2 = 93.6%; P = 0.000)
	Oba et al. (2020)	16 months (95% CI, 0-45; I^2 = 0.00%; P = 0.94)
	Vuong et al. (2019)	14.5 months (95% CI, 12.40-16.30 months)
Sunitinib	Efstathiadou et al. (2021)	16.50 months (95% CI, 2.45-30.55)
Objective Response (OR) = Complete Response (CR) and Partial Response (PR)		
Cabozantenib	Efstathiadou et al. (2021)	44.92% (95% CI, 38.64-51.20; I^2 = 0.00%; P = 0.575)
Lenvatinib	Efstathiadou et al. (2021)	44.07% (95% CI, 30.85-57.29)
Sorafenib	Efstathiadou et al. (2021)	48.39% (95% CI, 38.48-58.29; I^2 = 51.2%;P =0.056)
Pazopanib	Efstathiadou et al. (2021)	57.14% (95% CI, 39.98-74.30)
Sunitinib	Efstathiadou et al. (2021)	50.00% (95% CI, 29.93-70.07)
Sorafenib or Sunitinib	Efstathiadou et al. (2021)	71.43% (95% CI, 37.78-105.07)
Partial Response (PR)		
Sorafenib	Oba et al. (2020)	23% (95% CI, 1-45; I^2 = 0.00%; P = 0.61)
	Vuong et al. (2019)	21% (95% CI, 9-33; I^2 = 63%)
Overall Disease Progression (DP)		
Cabozantenib	Efstathiadou et al. (2021)	22.66% (95% CI, 17.41-27.90; I^2 =96.9%; P = 0.000)
Lenvatinib	Efstathiadou et al. (2021)	11.86% (95% CI, 2.85-20.87)
Sorafenib	Efstathiadou et al. (2021)	19.23% (95% CI, 10.44-28.02; I^2 = 59.7%; P = 0.030)
Pazopanib	Efstathiadou et al. (2021)	60.00% (95% CI, 42.99-77.01)
Sorafenib or Sunitinib	Efstathiadou et al. (2021)	14.29 % (95% CI, -14.47 to 43.04)
Stable Disease (SD)		
Cabozantenib	Efstathiadou et al. (2021)	27.73% (95% CI, 22.05-33.42; I^2 = 0.00%; P = 0.921)
Lenvatinib	Efstathiadou et al. (2021)	35.59% (95% CI, 22.80-48.38)
Sorafenib	Efstathiadou et al. (2021)	27.50% (95% CI, 17.78-37.22; I^2 = 52.4%; P = 0.062)

Drug	Study Citation	Treatment response
	Oba et al. (2020)	77.0% (95% CI, 45-100; I^2 = 48.9%; P = 0.42)
	Vuong et al. (2019)	58% (95% CI, 41-75; I^2 = 74%)
Pazopanib	Efstathiadou et al. (2021)	14.29% (95% CI, 1.56-27.01)
Sunitinib	Efstathiadou et al. (2021)	45.45% (95% CI, 28.44-62.47; I^2 = 64.0%; P = 0.096)
Sorafenib or Sunitinib	Efstathiadou et al. (2021)	14.29% (95% CI, -14.47 to 43.04)

CI = confidence interval; CR = complete response, DP = disease progression; HR = hazard ratio; OR = objective response; PFS = progression-free survival; PR = partial response; SD = stable disease; SR = systematic review.

Source: Information based on systematic reviews [1,26,27]

Appendix 8: Safety Outcomes of Systematic Reviews and Meta-Analysis

Note that this appendix has not been copy-edited.

Table 9: Systematic Reviews and Meta-Analysis Study Findings — Safety Outcomes

Drug	Study Citation	Treatment response
Drug discontinuation (% of patients)		
Cabozantenib	Efstathiadou et al. (2021)	54.79% (95% CI, 47.97-61.61)
Lenvatinib	Efstathiadou et al. (2021)	23.73% (95% CI, 12.24-35.21)
	Oba et al. (2020)	16% (95% CI, 7-15; I^2 = 0.00%; P = 0.71)
Sorafenib	Efstathiadou et al. (2021)	32.32% (95% CI, 24.25-40.40; I^2 =89.7%; P = 0.000)
	Oba et al. (2020)	16% (95% CI, 6-26; I^2 = 0.00%; P = 0.62)
	Vuong et al. (2019)	8% (95% CI, 2-15)
Pazopanib	Efstathiadou et al. (2021)	77.14% (95% CI, 62.29-92.00)
Grade>3 Adverse events (G3AEs - combined) (% of patients)		
Cabozantenib	Efstathiadou et al. (2021)	66.72% (95% CI, 60.75-72.68; I^2 = 0.00%; P = 0.505)
Lenvatinib	Efstathiadou et al. (2021)	55.93% (95% CI, 42.71 – 69.15)
Sorafenib	Efstathiadou et al. (2021)	52.63% (95% CI, 42.54-62.72; I^2 = 32.0%; P = 0.)
Pazopanib	Efstathiadou et al. (2021)	14.29% (95% CI, 1.56-27.01)
Grade 3, 4 Adverse events (G3AEs) (% of patients for each AE)		
Lenvatinib	Oba et al. (2020)	HFS: 3% (95% CI, 0–13; I^2 = 0%; P = 0.94) Hypertension: 28% (95% CI, 8–49; I^2 = 71.1%; P = 0.39) Proteinuria: 3% (95% CI, 0–13; I^2 = 0%; P = 0.33) Mucositis: 3% (95% CI, 0–13; I^2 = 0%; P = 0.76) Diarrhea: 9% (95% CI, 0–19; I^2 = 0%; P = 0.72) Fatigue: 9% (95% CI, 0–19; I^2 = 0%; P = 0.83) Weight loss: 9% (95% CI, 0–19; I^2 = 0%; P = 0.87) Rash: 3% (95% CI, 0–13; I^2 = 0%; P = 0.72) Anorexia: 2% (95% CI, 0–12; I^2 = 0%; P = 0.49)
Sorafenib	Oba et al. (2020)	HFS : 21% (95% CI, 11–31 ; I^2 = 0%; P = 0.99) Hypertension: 9% (95% CI, 0–19; I^2 = 0%; P = 0.91) Mucositis: 2% (95% CI, 0–12; I^2 = 0%; P = 0.86) Diarrhea: 5% (95% CI, 0–15; I^2 = 0%; P = 0.84) Fatigue: 7% (95% CI, 0–17; I^2 = 0%; P = 0.82) Weight loss: 5% (95% CI, 0–15; I^2 = 0%; P = 0.83) Rash: 6% (95% CI, 0–16; I^2 = 0%; P = 0.89) Anorexia: 2% (95% CI, 0–13; I^2 = 0%; P = 0.98)
	Vuong et al. (2019)	HFS: 18% (95% CI, 8-28; I^2 = 34) Diarrhea: 5% (95% CI, 0-10; I^2 = 0%) Skin Rash: 4% (95% CI, 0-7; I^2 = 0%) Weight loss: 4% (95% CI, 0-9; I^2 = 0%) Hypertension: 3% (95% CI, -1 to 7; I^2 = 0%)

Drug	Study Citation	Treatment response
		Mucositis: 3% (95% CI, -1 to 7; I^2 = 0%) Alopecia: 4% (95% CI, -1 to 8; I^2 = 0%) Anorexia: 4% (95% CI,-1 to 8; I^2 = 0%) Transaminase elevation: 3% (95% CI, -2 to 8; I^2 = 0%) Arthralgia/myalgias: 4% (95% CI, -2 to 10; I^2 = 0%)
Adverse events (% of patients for each AE)		
Lenvatinib	Oba et al. (2020)	HFS: 45% (95% CI, 9–80; I^2 = 90.1%; P = 0.61) Hypertension: 96% (95% CI, 59–100; I^2 = 90.9%; P = 0.59) Proteinuria 45% (95% CI, 9–80; I^2 = 90.9%; P = 0.33) Mucositis: 38% (95% CI, 24–51; I^2 = 35.5%; P = 0.82) Diarrhea: 75% (95% CI, 62–88; I^2 = 33.5%; P = 0.55) Fatigue: 70% (95% CI, 60–79; I^2 = 0.01%; P = 0.63) Weight loss: 53% (95% CI, 33–73; I^2 = 67.6%; P = 0.96) Rash: 14% (95% CI, 4–24; I^2 = 0%; P = 0.44) Anorexia: 67% (95% CI, 44–90; I^2 = 76.2%; P = 0.45) Alopecia: 13% (95% CI, 3–23; I^2 = 0%; P = 0.57)
Sorafenib	Oba et al. (2020)	HFS: 96% (95% CI, 86–100; I^2 = 0.4%; P = 0.49) Hypertension: 41% (95% CI, 31–51; I^2 =0.0%; P = 0.51) Mucositis: 30% (95% CI, 19–40; I^2 = 3.1%; P = 0.09) Diarrhea: 81% (95% CI, 69–92; I^2 = 12.5%; P = 0.08) Fatigue: 62% (95% CI, 41–84; I^2 = 67.1%; P = 0.42) Weight loss: 59% (95% CI, 38–79; I^2 = 67.1%; P = 0.30) Rash: 79% (95% CI, 54–100; I^2 = 77.2%; P = 0.56) Anorexia: 35% (95% CI, 17–53; I^2 = 39.2%; P = 0.46) Alopecia: 71% (95% CI, 55–87; I^2 = 24.1%; P = 0.21)
	Vuong et al. (2019)	HFS: 69% (95% CI, 53-85; I^2 =73%) Diarrhea: 49% (95% CI, 29-69; I^2 = 76%) Alopecia: 48% (95% CI19-78; I^2 = 87%) Mucositis: 40% (95% CI18-61; I^2 = 79%) Skin Rash: 39% (95% CI, 25-56; I^2 = 68%) Fatigue: 39% (95% CI, 22-57; I^2 = 72%) Hypertension: 35% (95% CI, 17-52; I^2 = 53%) Thyroid test dysfunction: 27% (95% CI, 10-44; I^2 = 0%) Transaminase elevation: 27% (95% CI, 1-52; I^2 = 77%) Arthralgia/myalgias: 26% (95% CI, -1 to 53; I^2 = 82%) Anorexia: 26% (95% CI, 15-37; I^2 = 0%) Weight loss: 25% (95% CI9-41; I^2 = 66%)

CI, = confidence interval; HFS = HFS = hand foot syndrome

Source: Information based on systematic reviews [1,26,27]

Appendix 9: Additional Safety Information

Note that this appendix has not been copy-edited.

Table 10: Additional Safety Information From Health Canada Product Labels

Drug	Serious AE	TEAEs
Lenvatinib	hypertension, renal failure and impairment, pulmonary embolism, cardiac failure, intracranial tumor haemorrhage, PRES / RPLS, hepatic failure, arterial thromboembolisms [cerebrovascular accident, transient ischaemic attack, and myocardial infarction], and gastrointestinal perforation and fistula.	≥30% in patients with DTC • hypertension, diarrhea, decreased appetite, decreased weight, nausea, fatigue, stomatitis, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia.
Pazopanib	hepatic effects, hypertension, QT prolongation and Torsade de Pointes, arterial and venous thrombotic events, cardiac dysfunction, hemorrhagic events and gastrointestinal perforation and fistula, venous thromboembolic events and pneumothorax	≥10% in patients with mRCC or STS • diarrhea, nausea, vomiting, abdominal pain, hypertension, fatigue, asthenia, hair color changes, anorexia, headache, weight decreased, tumor pain, dysgeusia, musculoskeletal pain, myalgia, gastrointestinal pain, dyspnea, exfoliative rash, cough, peripheral edema, alopecia, dizziness, skin disorder, skin hypopigmentation, stomatitis, chest pain.
Sorafenib	cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, and thromboembolism	≥20% in patients with HCC, RCC or DTC • diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash/desquamation, weight loss, anorexia, nausea, abdominal pain, hypertension, and hemorrhage
Sunitinib	left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function	≥20% in patients with GIST, mRCC or pancreatic NET • fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, anorexia, and bleeding.

DTC = Differentiated thyroid cancer; GIST = Gastrointestinal stromal tumour; HCC = Hepatocellular carcinoma; mRCC = Metastatic Renal Cell Carcinoma; NET = neuroendocrine tumours; RCC = Renal cell carcinoma; STS = Soft Tissue Sarcoma.

Source: Information based on Health Canada product labels[16,30,31,48]