Reimbursement Review

Provisional Funding Algorithm

Indication: Differentiated thyroid carcinoma

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

Background

Following a request from jurisdictions, CADTH will design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding statuses. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on differentiated thyroid carcinoma. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

This will be the first rapid provisional funding algorithm report for differentiated thyroid carcinoma to incorporate the CADTH recommendations for cabozantinib (Cabometyx) and lenvatinib (Lenvima), as well as selpercatinib (Retevmo) for *RET* fusion-positive differentiated thyroid carcinoma. The roles of larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) for *NTRK* gene fusion-positive differentiated thyroid carcinoma are also incorporated.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing

Cabozantinib (Cabometyx)	November 17, 2022	pERC recommends that cabozantinib be reimbursed for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory (RAI-R) or ineligible only if the conditions listed below are met:
		• Treatment with cabozantinib should be reimbursed in patients with DTC who meet all of the following criteria:
		  ○ refractory to prior RAI therapy or not eligible for RAI
		  ○ previously treated with 1 to 2 prior VEGFR-targeting TKIs
		  ○ have a good performance status.
		• Cabozantinib should be renewed for patients who exhibit a response to treatment and for whom treatment is tolerable.
		  ○ Response should be measured using clinical assessment, biochemical markers and radiological imaging.
		  ○ Patients should be assessed for treatment response every 3 to 4 months or as per physician discretion.
		• Cabozantinib should be discontinued if patients experience disease progression or unacceptable toxicity.
		• Patients should be under the care of an oncologist or endocrinologist with expertise in the management of thyroid cancer.
		• A reduction in price.

Entrectinib (Rozlytrek)	November 17, 2022	pERC recommends that entrectinib be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation only if the conditions listed below are met:
		• Patients should have all of the following:
		  ○ unresectable locally advanced or metastatic extracranial solid tumours, including patients with brain metastases
		  ○ *NTRK* gene fusion
		  ○ without a known acquired resistance mutation
		  ○ good performance status.
		• Reimbursement should be limited to adults ≥ 18 years of age.
		• All available standard treatments for that tumour site should have been previously used and exhausted.
		• Reimbursement with entrectinib should not be initiated in patients who have primary CNS tumours but may be provided for those with controlled or asymptomatic CNS metastases.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing

		• Reimbursement with entrectinib should not be initiated in patients who have received prior treatment with an *NTRK* inhibitor.
		• Assessment for renewal of entrectinib should be based on radiographic evaluation (CT and/or MRI):
		  ○ every 3 to 4 months for the first year after treatment initiation
		  ○ longer interval follow-up may be continued thereafter based on clinical judgment.
		• Reimbursement should be discontinued upon the occurrence of any of the following:
		  ○ radiographic disease progression
		  ○ unacceptable toxicity.
		• Entrectinib should only be prescribed by a clinician experienced in diagnosing and treating patients with *NTRK* gene fusions.
		• Entrectinib should only be administered as monotherapy and should not be given in combination with other systemic anticancer therapies.
		• A reduction in price
		• The feasibility of adoption of entrectinib must be addressed.

Selpercatinib (Retevmo)	July 18, 2022	pERC recommends that selpercatinib be reimbursed for the treatment of adult patients with *RET* fusion-positive DTC with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib only if the following conditions are met: • Treatment with selpercatinib should be reimbursed in adult patients with *RET* fusion-positive DTC with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib. • Patients must have good performance status. • Selpercatinib should be renewed for patients who exhibit a response to treatment, as per physician discretion, and for whom treatment is tolerable. • Patients should be assessed for treatment response every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to 16 weeks or as per physician discretion. • Selpercatinib should be prescribed by clinicians with expertise in the management of thyroid cancer. • Selpercatinib should not be reimbursed if given in combination with other systemic anticancer drugs. • A reduction in price. • Access to *RET* testing. **Guidance on sequencing:** • The clinical experts considered that for the denomination "not amenable to surgery or radioactive iodine," it is sensible to include patients who are refractory to RAI and/or unable to undergo surgery. pERC agreed that reimbursement of selpercatinib should include patients who are unable to receive RAI therapy due to a contraindication. • Should patients who are intolerant to first-line therapy with sorafenib or lenvatinib be eligible for treatment with selpercatinib? ○ Yes, patients in this category should be able to receive selpercatinib. Experts emphasized that sorafenib is not funded in Canada. pERC agreed that reimbursement of selpercatinib should include patients who are intolerant to first-line therapy with sorafenib or lenvatinib.

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		• Is the efficacy of selpercatinib expected to be similar across the subtypes of DTC?
		  ○ The experts mentioned that efficacy should be similar across subtypes of DTC if they are selected according to the mutation status (i.e., according to the driver mutation). pERC agreed with the clinical experts.
		• Should patients currently being treated with lenvatinib or sorafenib in the second line who have not progressed, but are known or found to have *RET* fusion, be eligible to switch to selpercatinib (assuming all other criteria are met)?
		  ○ pERC noted that the clinical experts "yes, it would be reasonable to proceed, according to the clinical experts." While pERC agreed with the clinical experts, pERC expressed that patients can also remain on lenvatinib or sorafenib and switch to selpercatinib once they have progressed.

Larotrectinib (Vitrakvi)	November 22, 2021	pERC recommends that larotrectinib should be reimbursed for the treatment of adult and pediatric patients with metastatic or locally advanced solid tumours who have a *neurotrophic tyrosine receptor kinase (NTRK)* gene fusion only if the following conditions are met:
		• Patients should have the following:
		  ○ NTRK gene fusion without a known acquired resistance mutation
		  ○ metastatic or locally advanced unresectable solid tumour
		  ○ good performance status defined as:
		  ▪ ECOG PS 0 to 2 (adults)
		  ▪ ECOG PS 0 to 3 (pediatrics).
		• All available standard treatments for that tumour site should have been previously used and exhausted and surgery and/or radiation would lead to substantial morbidity.
		• Treatment with larotrectinib should not be initiated in patients who:
		  ○ have symptomatic brain metastases
		  ○ have unstable cardiovascular disease, or
		  ○ are unable to discontinue treatment with a strong CYP3A4 inhibitor or inducer before treatment initiation.
		• Treatment with additional cycles of larotrectinib should be permitted unless either of the following occurs:
		  ○ radiographic disease progression
		  ○ unacceptable toxicity.
		• Assessment for renewal of larotrectinib should be based on radiographic evaluation (CT and/or MRI) every 3 to 4 months for the first year after treatment initiation. Longer interval follow-up may be continued thereafter based on clinical judgment.
		• Treatment with larotrectinib should be discontinued upon the occurrence of any of the following:
		  ○ radiographic disease progression
		  ○ unacceptable toxicity
		  ○ development of adverse reactions that do not resolve within 4 weeks of withholding the drug.
		• Larotrectinib should only be prescribed by a clinician experienced in diagnosing and treating patients with *NTRK* gene fusions
		• Larotrectinib should only be administered under the supervision of a health professional experienced in the use of antineoplastic drugs
		• Larotrectinib should be administered as monotherapy

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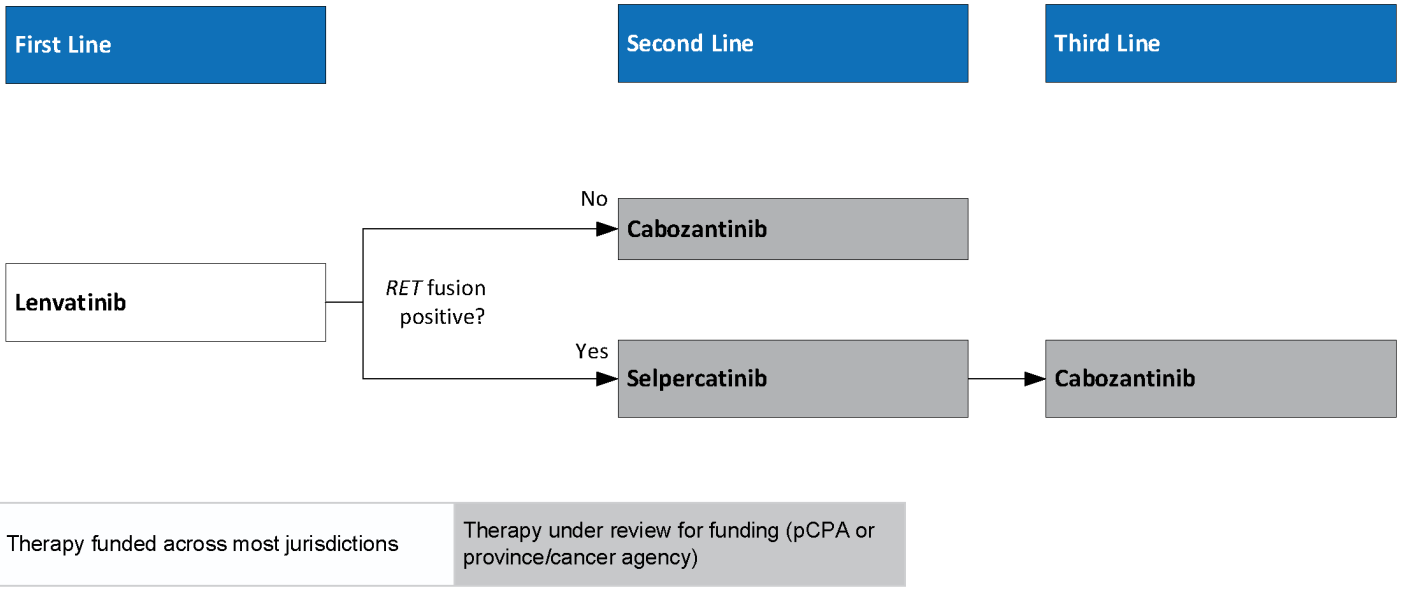
		• Dosing of larotrectinib should be as follows:
		  ○ 100 mg (oral dose) twice daily in individuals with BSA ≥ 1 m^2, or
		  ○ 100 mg/m^2 (oral dose) twice daily for children with a BSA < 1 m^2.
		• Price reduction is needed.

Lenvatinib (Lenvima)	September 20, 2016	pERC recommends reimbursement of lenvatinib (Lenvima) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC) conditional on the cost-effectiveness being improved to an acceptable level. Treatment should be for patients with a good performance status and who otherwise meet the eligibility criteria for the SELECT trial, and should continue until disease progression or unacceptable toxicity.
Sorafenib (Nexavar)	July 16, 2015	pERC does not recommend funding sorafenib (Nexavar) in patients with locally advanced or metastatic differentiated thyroid cancer progressing after treatment with radioactive iodine. The committee made this recommendation because they were unable to conclude that there was a net clinical benefit with sorafenib compared to placebo in this population.

BSA = baseline serum albumin; CNS = central nervous system; DTC = differentiated thyroid carcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; RAI = radioactive iodine-refractory; RAI-R = radioactive iodine-refractory; TKI = Tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Differentiated Thyroid Carcinoma



pCPA = pan-Canadian Pharmaceutical Alliance.
Notes: This algorithm refers to treatment of the unresectable, radioactive iodine-refractory differentiated thyroid carcinoma setting.
Selpercatinib may be funded for patients who are intolerant to first-line therapy with lenvatinib.
For patients who are also positive for *NTRK* fusion, *NTRK* inhibitors (e.g., larotrectinib, entrectinib) may be funded when all available standard treatments have been previously used and exhausted.

Description of the Provisional Funding Algorithm

Differentiated Thyroid Carcinoma

For individuals who have unresectable, radioactive iodine-refractory differentiated thyroid carcinoma, their first-line option is lenvatinib.

As a second-line option, it would depend on whether the individual has *RET* fusion-positive differentiated thyroid carcinoma or not.

For those individuals without *RET* fusion-positive differentiated thyroid carcinoma, the second-line option is cabozantinib.

For individuals with *RET* fusion-positive differentiated thyroid carcinoma, the second-line option is selpercatinib followed by the third-line option of cabozantinib.

For individuals with *NTRK* gene-positive differentiated thyroid carcinoma, the *NTRK* inhibitors larotrectinib and entrectinib may be funded when all available standard treatments have been previously used and exhausted.