Draft Reimbursement Recommendation

Dabrafenib-Trametinib

Reimbursement request: For the treatment of unresectable or metastatic *BRAF* V600 mutant anaplastic thyroid cancer
Requester: Public drug programs
Draft recommendation: Reimburse with conditions

Summary

What is the Reimbursement Recommendation for Dabrafenib-Trametinib?

The Formulary Management Expert Committee (FMEC) recommends that dabrafenib-trametinib, be reimbursed in adults for the treatment of unresectable or metastatic *BRAF* V600 mutant anaplastic thyroid cancer, provided certain conditions are met.

What Are the Conditions for Reimbursement?

Dabrafenib-trametinib should only be reimbursed in adult patients with unresectable or metastatic *BRAF* V600 mutant anaplastic thyroid cancer with good performance status. Note that a reduction in the prices of dabrafenib-trametinib may be required.

Why Did CDA-AMC Make This Recommendation?

FMEC reviewed a phase II, nonrandomized, single arm, open-label (ROAR) trial and a retrospective single arm chart review study, identified by CDA-AMC's systematic review of the literature. FMEC also considered input received from public drug programs.

FMEC concluded that there was uncertainty in the clinical value demonstrated by dabrafenib-trametinib. However, given there are no currently effective treatments for anaplastic thyroid cancer and it is high associated with high morbidity and mortality, FMEC concluded that dabrafenib-trametinib addresses a significant unmet clinical need for new treatments. The reimbursement conditions were further developed based on distinct social and ethical considerations, economic considerations and impacts on health systems.

The reimbursement of dabrafenib plus trametinib for adult patients with BRAF V600 anaplastic thyroid cancer with no standard locally or regionally available treatment options is expected to increase drug acquisition costs.

Therapeutic Landscape

What Is *BRAF* V600E Mutant Anaplastic Thyroid Cancer?

Anaplastic thyroid cancer (ATC) is an undifferentiated form of a tumour of the thyroid follicular epithelium and is most the aggressive type of thyroid cancer. ATC is rare, accounting for only about 1% of all thyroid cancers in Canada. It is the most lethal form of thyroid cancer which is frequently diagnosed at an advanced stage.

Recent advances in molecular profiling have shown that B-Raf kinase (BRAF) V600E mutation is present in 20% to 50% of ATC cases. However, depending on the assay method (immunohistochemistry versus RNA/DNA based techniques), other BRAF codon 600 mutations such as V600K and V600R can also be detected. In patients with locally advanced or metastatic ATC, the prognosis is extremely poor with a median survival from diagnosis is about 5 months, and 1-year survival rate is only 20%.

What Are the Current Treatment Options?

There are no effective therapies for ATC. Despite multimodal therapy being available, including surgery, external beam radiation, and systemic chemotherapy, the response rates are very low (< 15%).

What Is the Treatment Under Review?

Dabrafenib is a *BRAF*-kinase inhibitor and trametinib is a protein kinase inhibitor against the enzymes of MEK-1 and MEK-2. Dabrafenib--trametinib is approved by Health Canada for other indications including those with BRAF V600 mutations in adjuvant or metastatic melanoma, non-small cell lung cancers and low- or high-grade gliomas and is used as off label for *BRAF* V600 mutant anaplastic thyroid cancer in Canada.

Why Did We Conduct This Review?

While dabrafenib-trametinib is used off label for *BRAF* V600 mutant anaplastic thyroid cancer in Canada, it is approved by the US Food and Drug Administration and other countries. Given the poor prognosis of *BRAF* V600 mutant anaplastic thyroid cancer, additional and effective treatments are urgently needed to prolong life, delay disease progression and reduce the severity of symptoms.

Given the data protection for dabrafenib-trametinib has ended in 2021, this treatment is eligible for a non-sponsored reimbursement review as per the procedures for reimbursement reviews. At the request of the participating public drug programs, we reviewed the combination dabrafenib and trametinib to inform an Expert Committee recommendation on whether it should be reimbursed for patients with *BRAF* V600E mutant ATC.

Input From Community Partners

- **Public drug plans** inquired about the evidence for dabrafenib-trametinib to inform a recommendation on whether it should be reimbursed for adults with anaplastic thyroid cancer. The public drug plans outlined implementation questions related to treatment eligibility and potential costs
- We did not receive input from clinician groups or patient advocacy groups.

► **Refer to the main report and the supplemental material document for this review.**

Person With Lived Experience

A Person with Lived Experience in Ontario and his wife shared their journey with anaplastic thyroid cancer after a diagnosis in 2022. After experiencing neck discomfort and swelling, his condition deteriorated rapidly leading to hospitalization for over a year. He underwent emergency surgery and received radiation therapy with little success. As his symptoms worsened, he required a tracheostomy and a G-tube for nutrition. Doctors initially gave him three months to live, but genetic testing revealed he had the BRAF V600E mutation, leading to initiating treatment with dabrafenib and trametinib. Within weeks, his swelling reduced, his mobility increased, and they noted a significant improvement in their quality of life compared to chemotherapy. He remains on the treatment without the need for a G-tube, and other than fatigue and slight pain, he has minimal side effects compared to radiation, which he described as an acceptable trade-off for him to be present for his family.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person or caregiver might go through when facing this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework prior to developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, please refer to the Expert Committee Deliberation at Canada's Drug Agency document.

FMEC considered the following key discussion points, organized by the five domains of value.

Clinical Value

- **FMEC concluded that it is uncertain whether dabrafenib-trametinib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**
- **FMEC** members highlighted the following points:
    - FMEC discussed that given the rarity of this condition, the results from the ROAR trial likely represent the best available evidence. FMEC highlighted that all the outcomes assessed in the ROAR trial (ORR, DoR, PFS, OS and safety) are important. However, there is a lack of evidence for important outcomes such as the HRQoL. Further, there is a lack of details on impact to the disease burden, such as outcomes to measure the delay in requiring certain procedures (e.g., tracheostomy), duration of hospitalization and improvement in feeding functions.
    - FMEC discussed that the clinical effects are meaningful. Based on the ROAR trial with a median follow-up of 11.1 months, the overall response rate was 56% (95% CI 38.1 to 72.1) and the overall survival at 12 month was 51.7% (95% CI 33.6 to 67.1). While there is no direct evidence, the results appear to be promising.
    - FMEC discussed the evidence is of low certainty given the absence of direct comparators and non-randomized single arm study design (ROAR trial).

Unmet Clinical Need

- **FMEC concluded that there is significant unmet clinical need arising from anaplastic thyroid cancer despite available treatments.**
- Through reflection on the insights shared by people with lived experience, FMEC members noted the following important patient values or perspectives: There is no specific treatment for this rare and fatal disease. There is a need for more satisfactory treatments to prolong life, delay progression, reduce disease symptoms, minimize harms, improve QoL and reduce hospitalizations.
- **FMEC** members highlighted the following discussion points:

- FMEC also discussed the rarity of ATC, accounting for only 1% of all thyroid cancers in Canada. The median survival for ATC is 5 to 6 months after diagnosis and 1-year overall survival is less than 20%. All patients with ATC are diagnosed as stage IV due to the aggressive nature of the condition. Further, the response rates to standard systemic therapy are low (<15%). There is substantial mortality and morbidity with this condition.

- FMEC discussed that in the setting of BRAF V600 mutant anaplastic thyroid cancer, there is a clear unmet clinical need given there are currently no effective or safe alternative treatments. FMEC acknowledged that while the evidence reviewed was exclusive to patients with BRAF V600E mutations, the biology of other BRAF mutants would not be expected to behave differently. FMEC agreed with the guest specialists that it is highly unlikely that a clinical trial for patients with other BRAF V600 mutations would be conducted, further emphasizing the unmet clinical need in this subpopulation.

Distinct Social and Ethical Considerations

- **FMEC concluded that dabrafenib-trametinib would potentially address a significant nonclinical need arising from anaplastic thyroid cancer. FMEC concluded that there are important measures that should be implemented to ensure that the use of dabrafenib-trametinib addresses relevant social and ethical implications.**

- **FMEC** members highlighted the following points:

    - FMEC discussed there are non-clinical needs that may arise from disease progression due to the lack of effective treatment options. The ensuing complications such as airway obstruction or dysphagia often necessitate home care support and other management (e.g. tracheostomy, gastrostomy tube feeding). The oral formulation of dabrafenib-trametinib may alleviate resources related to alternative treatment options such as intravenous chemotherapies. These chemotherapeutic options are ineffective, toxic, and are associated with high treatment burden on patients, family and caregivers.

    - FMEC noted that the cost of oral medications is variable across jurisdictions and presents a concern for inequity. These treatments should be available for all patients regardless of where they reside within Canada.

    - FMEC also discussed for patients requiring g-tube administration of dabrafenib where a liquid formulation is not available, the potential challenges with dissolving a large number of tablets for administration (e.g., 15 tablets for 10mg dissolving tablets for 150mg dosage) on a daily basis can pose undue burden on patients and caregivers.

Economic Considerations

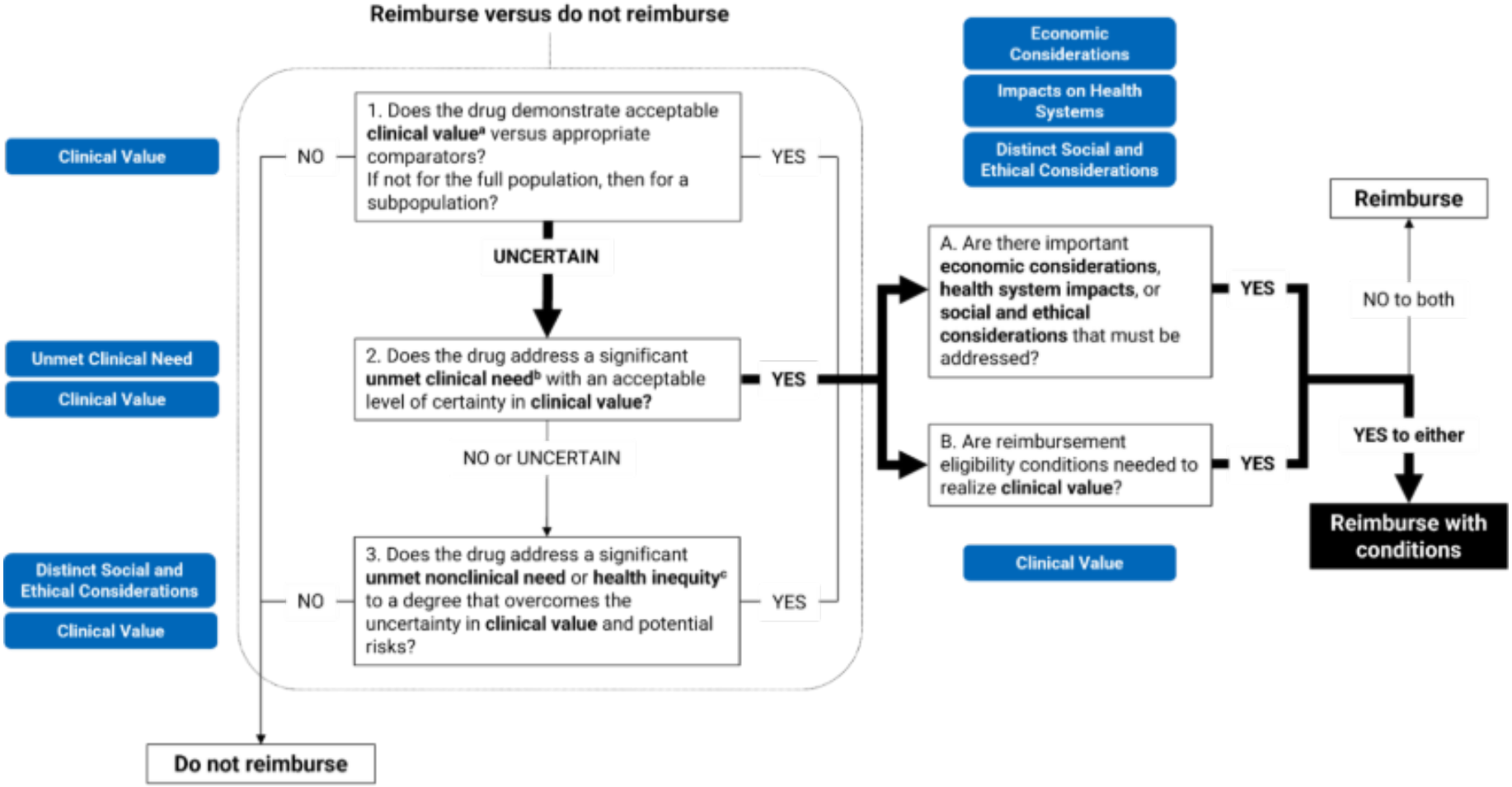
- **FMEC concluded that there are economic considerations that are important to address when implementing dabrafenib-trametinib.**
- **FMEC** members highlighted the following points:
    - The reimbursement of dabrafenib plus trametinib for the treatment of adult patients with BRAF V600 ATC is expected to increase overall drug acquisition costs.
    - No evidence was identified regarding the cost-effectiveness of dabrafenib plus trametinib relative to no active treatment for adult patients with BRAF V600E anaplastic thyroid cancer with no standard locally or regionally available treatment options in Canada, and therefore, estimates of cost-effectiveness were not available to the committee. FMEC discussed that a cost-effectiveness analysis would be valuable to fully inform the reimbursement recommendation.
    - Given that dabrafenib plus trametinib is associated with increased drug acquisition costs and likely, but uncertain, clinical benefit relative to no active treatment, FMEC recommended price reductions.
    - FMEC heard from the clinical experts that BRAF V600 mutation testing is available and conducted across jurisdictions; therefore, its associated costs are unlikely to represent an incremental expense.
    - FMEC noted that both drugs are approaching the end of their market exclusivity, which may lead to the availability of generic products and exert downward pressure on market prices. The patent for trametinib is set to expire in mid-2025, while the patent for dabrafenib is expected to expire in 2029.

Impacts on Health Systems

- **FMEC concluded that it is uncertain whether there are impacts on health systems that are important to address when implementing dabrafenib-trametinib.**
- **FMEC** members highlighted the following points:
    - FMEC discussed that treatment with dabrafenib-trametinib requires expedited access to specialized cancer centers. Rapid specialized testing with *BRAF* V600 as well as access to timely results are important implementation considerations.
    - FMEC also discussed that implementing dabrafenib-trametinib is unlikely to have immediate impacts on health systems. However given the potential for improved survival with treatment, there are possible implications for additional health care resources.

Figure 1: Recommendation Pathway

Alt-text: Flow chart indicating the steps used by the committee for this recommendation. The committee determined that it was uncertain whether the drug demonstrated acceptable clinical value versus appropriate comparators. However, the committee also determined that the drug addresses a significant unmet clinical need with an acceptable level of certainty in clinical value. Therefore, the committee recommended reimbursement of the drug for the patient population under consideration. After deliberating on economic considerations, impacts on health systems, distinct social and ethical considerations, and whether reimbursement conditions are needed to realize clinical value, the committee determined that reimbursement of the drug should be contingent upon 1 or more conditions being satisfied.



a Acceptable clinical value refers to at least comparable clinical value (if the drug is expected to be substitutive treatment) or added clinical value (if the drug is expected to be additive treatment) versus appropriate comparators.

b Significant unmet clinical need depends on all of the following: severity of the condition, availability of effective treatments, and challenges in evidence generation due to rarity of the condition or ethical issues.

c Unmet nonclinical need and health inequity are key components within the distinct and social ethical considerations domain of value.

Full Recommendation

With a vote of 8 to 0, FMEC recommends that dabrafenib-trametinib, for the treatment of adult patients with unresectable or metastatic *BRAF* V600 mutant anaplastic thyroid cancer, be reimbursed if the conditions presented in Table 1 are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Dabrafenib-trametinib may be initiated in adults with confirmed *BRAF* V600 mutant ATC and good performance status.	The evidence from ROAR trial reported that dabrafenib-trametinib improved clinical outcomes including overall response rate, duration of response, progression free survival and overall survival. The initiation condition aligns with the ROAR trial inclusion criteria relevant to ATC.	It is critical to allow rapid access to treatment which is essential in managing *BRAF* V600 ATC. BRAF V600 should be tested and confirmed by available and approved methods as feasible in local practices.
Discontinuation and renewal		
3. Dabrafenib-trametinib should be discontinued if there is disease progression or significant toxicity.	Consistent with clinical practice, patients in the ROAR trial discontinued treatment upon disease progression or significant toxicity.	Response should be monitored by ATC specialist teams.
Prescribing		
4. Prescribing should be limited to clinicians with expertise in the diagnosis and management of ATC.	This will ensure that appropriate treatment is prescribed for patients and adverse events are optimally managed.	

Reimbursement condition	Reason	Implementation guidance
Pricing		
5. A reduction in the prices of dabrafenib and trametinib may be required.	The reimbursement of dabrafenib plus trametinib for the treatment of adult patients with BRAF V600E-mutant ATC is expected to increase overall drug acquisition costs. No evidence was identified regarding the cost-effectiveness of dabrafenib plus trametinib relative to no active treatment for BRAF V600E-mutant ATC in Canada. Therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether dabrafenib plus trametinib is cost-effective. Given that dabrafenib plus trametinib is associated with increased drug acquisition costs and likely clinical benefit relative to no active treatment, price reductions may be required.	

Abbreviation: ATC = anaplastic thyroid cancer

Feedback on Draft Recommendation

<to be updated after the feedback period>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and two guest specialists from Ontario.

Meeting date: March 20, 2025

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the people with lived experience who presented directly to FMEC, and to patient organizations representing the community of those living with Thyroid Cancer, including the Thyroid Foundation of Canada, and particularly Laz Bouros, Hodjat & Dora Firoozi.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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