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

May 2025

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Dabrafenib Plus Trametinib

Reimbursement request: For the treatment of unresectable or metastatic *BRAF* V600 mutant anaplastic thyroid cancer

Requester: Public drug programs

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Dabrafenib Plus Trametinib?

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

What Are the Conditions for Reimbursement?

Dabrafenib plus trametinib should only be reimbursed in adults with unresectable or metastatic *BRAF* V600 mutant ATC with good performance status. Note that a reduction in the prices of dabrafenib plus trametinib may be required.

Why Did Canada's Drug Agency Make This Recommendation?

FMEC reviewed a phase II, nonrandomized, single-arm, open-label trial (ROAR) and a retrospective single-arm chart review study identified by the Canada's Drug Agency (CDA-AMC) 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 plus trametinib. However, given there are no currently effective treatments for ATC and it is associated with high morbidity and mortality, FMEC concluded that dabrafenib plus 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 adults with *BRAF* V600 ATC with no standard locally or regionally available treatment options is expected to increase drug acquisition costs.

Therapeutic Landscape

What Is *BRAF* V600E Mutant ATC?

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 and is frequently diagnosed at an advanced stage.

Recent advances in molecular profiling have shown that a *BRAF* V600E mutation is present in 20% to 50% of ATC cases. However, depending on the assay method (immunohistochemistry versus ribonucleic acid– or DNA-based techniques), other *BRAF* codon 600 mutations, such as V600K and V600R, can also be detected. The prognosis for patients with locally advanced or metastatic ATC is extremely poor, with a median survival from diagnosis of about 5 months and a 1-year survival rate of 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, response rates are very low (below 15%).

What Is the Treatment Under Review?

Dabrafenib is a *BRAF*-kinase inhibitor and trametinib is a protein kinase inhibitor against the MEK-1 and MEK-2 enzymes. Dabrafenib plus 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 off label for *BRAF* V600 mutant ATC in Canada.

Why Did We Conduct This Review?

While dabrafenib plus trametinib is used off label for *BRAF* V600 mutant ATC in Canada, it is approved by the US FDA and other countries. Given the poor prognosis for patients with *BRAF* V600 mutant ATC, 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 plus trametinib ended in 2021, this treatment is eligible for a nonsponsored reimbursement review, per the Procedures for Reimbursement Reviews. At the request of the participating public drug programs, we reviewed the combination dabrafenib plus 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 plus trametinib to inform a recommendation on whether it should be reimbursed for adults with ATC. 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 for this review.

►**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 ATC after a diagnosis in 2022. After experiencing neck discomfort and swelling, his condition deteriorated rapidly, leading to hospitalization for more than a year. He underwent emergency surgery and received radiation therapy with little success. As his symptoms worsened, he required a tracheostomy and a gastrostomy tube for nutrition. Doctors initially gave him 3 months to live, but genetic testing revealed he had the *BRAF* V600E mutation, leading to initiating treatment with dabrafenib plus trametinib. Within weeks, his swelling reduced, his mobility increased, and they noted a significant improvement in their quality of life compared to treatment with chemotherapy. He remains on the treatment without the need for a gastrostomy tube, and other than fatigue and slight pain, he has minimal side effects compared to treatment with 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 before developing its 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 5 domains of value.

Clinical Value

- **FMEC concluded that it is uncertain whether dabrafenib plus 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 (overall response rate, duration of response, progression-free survival, overall survival and safety) are important. However, there is a lack of evidence for important outcomes such as health-related quality of life. Further, there is a lack of detail on impact to 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% confidence interval, 38.1 to 72.1) and the overall survival at 12 months was 51.7% (95% confidence interval, 33.6 to 67.1). While there is no direct evidence, the results appear to be promising.
- FMEC discussed that the evidence is of low certainty given the absence of direct comparators and the nonrandomized single-arm study design (ROAR trial).

Unmet Clinical Need

- **FMEC concluded that there is significant unmet clinical need arising from ATC 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, and there is a need for more satisfactory treatments to prolong life, delay progression, reduce disease symptoms, minimize harms, improve quality of life, and reduce hospitalizations.
- FMEC members highlighted the following discussion points:
  - FMEC discussed the rarity of ATC, which accounts 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%) and there is substantial mortality and morbidity with this condition.
  - FMEC also discussed that in the setting of *BRAF* V600 mutant ATC, 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, other *BRAF* mutations 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 plus trametinib would potentially address a significant nonclinical need arising from ATC. FMEC concluded that there are important measures that should be implemented to ensure that the use of dabrafenib plus trametinib addresses relevant social and ethical implications.**
- FMEC members highlighted the following points:
  - FMEC discussed there are nonclinical 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 plus trametinib may alleviate resources related to alternative treatment options, such as IV chemotherapies. These chemotherapeutic options are ineffective, toxic, and associated with high treatment burden on patients, families, 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 that, for patients requiring gastrostomy 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 10 mg dissolving tablets for 150 mg dosage) on a daily basis can pose undue burden on patients and caregivers.

Economic Considerations

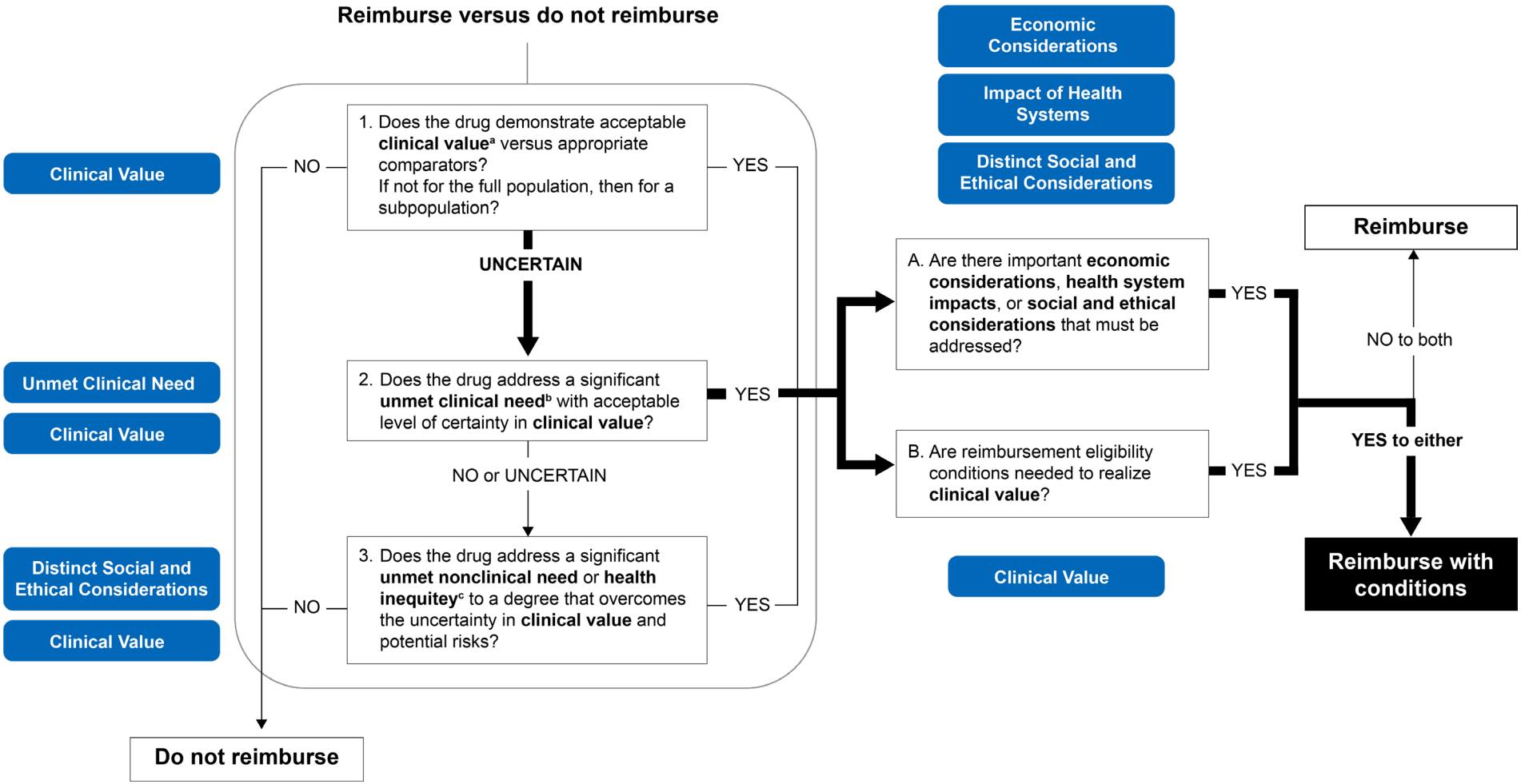
- **FMEC concluded that there are economic considerations that are important to address when implementing dabrafenib plus trametinib.**
- FMEC members highlighted the following points:
  - The reimbursement of dabrafenib plus trametinib for the treatment of adults with *BRAF* V600 ATC is expected to increase overall drug acquisition costs.
  - No evidence was identified regarding the cost-effectiveness of dabrafenib plus trametinib relative to no active treatment for adults with *BRAF* V600E ATC with no standard locally or regionally available treatment options in Canada; 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 plus trametinib.**
- FMEC members highlighted the following points:
  - FMEC discussed that treatment with dabrafenib plus trametinib requires expedited access to specialized cancer centres. Rapid specialized testing for *BRAF* V600 as well as access to timely results are important implementation considerations.
  - FMEC also discussed that implementing dabrafenib plus 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



[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 plus trametinib, for the treatment of adults with unresectable or metastatic *BRAF* V600 mutant ATC, 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 plus trametinib may be initiated in adults with confirmed *BRAF* V600 mutant ATC and good performance status.	The evidence from the ROAR trial indicated that dabrafenib plus 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.	*BRAF* V600 testing is required to determine if patients are eligible for treatment with dabrafenib plus trametinib. It is critical to allow rapid access to treatment that is essential in managing *BRAF* V600 ATC. *BRAF* V600 should be tested and confirmed by available and approved methods as feasible in local practices. Note that while good performance status is an initiation condition, patients with airway obstruction related to the tumour could potentially still be eligible to start dabrafenib plus trametinib therapy.
Discontinuation and renewal		
2. Dabrafenib plus 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		
3. 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.	—
Pricing		
4. A reduction in the prices of dabrafenib plus trametinib may be required.	The reimbursement of dabrafenib plus trametinib for the treatment of adults 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.	—

Reimbursement condition	Reason	Implementation guidance
	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.	

ATC = anaplastic thyroid cancer.

Feedback on Draft Recommendation

Public drug programs have reviewed the draft recommendations and provided minor editorial suggestions that have been incorporated. A clinician group from Ontario Health (Cancer Care Ontario) – Head and Neck Cancer Drug Advisory Committee also submitted feedback. This group shared support for the recommendation and provided some suggestions for revisions for the reimbursement conditions.

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 2 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 Firoozi, and 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 the 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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