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

Reimbursement Review

Review Report

DABRAFENIB PLUS TRAMETINIB

(Non-Sponsored Review)

Therapeutic area: *BRAF* V600E mutant anaplastic thyroid cancer

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Key Messages

What is Anaplastic Thyroid Cancer?

- Anaplastic thyroid cancer (ATC) is an undifferentiated form of tumour of the thyroid follicular epithelium, and most aggressive type of thyroid cancer, with the prognosis being extremely poor.
- 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.

What are the Treatment Goals and Current Treatment Options for Anaplastic Thyroid Cancer?

- The primary goal for treatment of patients with *BRAF* V600E mutant ATC is to prolong life, delay disease progression, reduce severity of symptoms, minimize adverse events (AEs), and improve quality of life.
- There are no effective therapies for ACT. Despite multimodal therapy being available, including surgery, external beam radiation, and systemic chemotherapy, the response rates are very low.

What is Dabrafenib plus Trametinib and Why Did We Conduct This Review?

- Dabrafenib is a BRAF-kinase inhibitor and trametinib is a protein kinase inhibitor against the enzymes MEK-1 and MEK-2. The combination of dabrafenib and trametinib has been approved in the US and Europe for the treatment of BRAF-mutated melanoma and ATC.
- In patients with locally advanced or metastatic *BRAF* V600E mutant ATC, the prognosis is extremely poor with a median survival from diagnosis is about 5 months, and 1-year survival rate is only 20%. Currently, there is no specific treatment for ATC and most patients are managed by best supportive care or palliative radiotherapy.
- At the request of the participating public drug programs, we reviewed dabrafenib plus trametinib to inform a recommendation on whether it should be reimbursed for patients with *BRAF* V600E mutant ATC.

How Did We Evaluate Dabrafenib plus Trametinib?

- We reviewed the clinical evidence on the beneficial and harmful effects and cost-effectiveness of dabrafenib and trametinib combination therapy used in Canada for the treatment of patients with *BRAF* V600E mutant ATC.
- The clinical evidence was identified through systematic searches for available studies. We consulted 2 clinical specialists with expertise in the diagnosis and management of ATC as part of the review process.

What Did We Find?

Clinical Evidence

- We reviewed a phase II, nonrandomized, single arm, open-label (ROAR) trial and a retrospective single arm chart review study, describing the efficacy and safety of combination dabrafenib and trametinib therapy in patients with *BRAF* V600E mutant ATC.
- The ROAR trial reported that combination dabrafenib and trametinib therapy improved clinical outcomes, including overall response rate (ORR), duration of response (DoR), progression free survival (PFS) and overall survival (OS).
- The retrospective single arm chart review study also reported an improvement in ORR, but with a shorter median duration of PFS and OS compared to the ROAR trial.
- The safety profile was consistent with the established tolerability of dabrafenib and trametinib, and no new AEs were detected.

Economic Evidence

- Reimbursing dabrafenib plus trametinib for adult patients with BRAF V600E anaplastic thyroid cancer with no standard locally or regionally available treatment options is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
ATC	anaplastic thyroid cancer
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
ITT	intention-to-treat
PFS	progression free survival
ORR	overall response rate
OS	overall survival

BACKGROUND

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of dabrafenib plus trametinib in the treatment of patients with *BRAF* V600E mutant anaplastic thyroid cancer (ATC) with no satisfactory alternative treatment options available.

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Dabrafenib capsules, 50 mg and 75 mg, oral. Trametinib tablets, 0.5 mg and 2 mg, oral. Trametinib powder for solution, 4.7 mg/bottle (0.05 mg/mL after reconstitution), oral.
Relevant Health Canada indication	Not applicable
Mechanism of action	Dabrafenib is a B-Raf (*BRAF*) kinase inhibitor. Trametinib is a mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor.
Recommended dosage	Dabrafenib: 150 mg twice daily[a] Trametinib: 2 mg once daily[a]
Data protection status	Dabrafenib mesylate data protection has ended on 2021-07-16 Trametinib: data protection has ended on 2021-07-18
Status of generic drugs / biosimilars	None available
Information on the CDA-AMC review	
Requestor	Cancer Care Ontario
Indication under consideration for reimbursement	*BRAF* V600E mutant ATC
Clinical review focus	Population: Adults with unresectable or metastatic *BRAF* V600E mutant ATC. Intervention: Dabrafenib (150 mg twice daily) and trametinib (2mg once daily) given continuously until disease progression, death, or discontinuation for any other reasons. Comparators: Best supportive care or no treatment Outcomes: • Efficacy: ORR, DoR, PFS, and OS, HRQoL. • Safety: Any AEs, treatment-related AEs, AEs leading to discontinuation, serious AEs, and death.

AE = adverse events; ATC = anaplastic thyroid cancer; CR = complete response; DoR = duration of response; HRQoL = health-related quality of life; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase kinase; ORR = overall response rate; PFS = progression-free survival; PR = partial response; OS = overall survival.

[a] Based on clinical trial (not from Health Canada indication).

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-sponsored Reimbursement Review. However, we received no clinician or patient group input in this review.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two oncologists with expertise in the diagnosis and management of ATC participated as part of the review team, with representation from Ontario.

Disease Background

ATC is an undifferentiated form of tumour of the thyroid follicular epithelium.[1] It is rare, accounting for only 1% of all thyroid cancers in Canada, but is the most aggressive type of thyroid cancer, with extremely poor treatment outcomes.[2] The median survival for ATC is 5 to 6 months after diagnosis, and 1-year overall survival is less than 20%.[3] ATC tends to occur in patients over 60 years old, and more likely affects females than males.[4]

All patients with ATC are diagnosed as stage IV due to its aggressive nature (stage IVa: confined in thyroid gland, 10% diagnosed; stage IVb: extension outside of the thyroid or cervical lymph nodes, 40% diagnosed; stage IVc: distant metastasis, 50% diagnosed).[4] Recent advances in molecular profiling have shown that B-Raf kinase (*BRAF*) V600E mutation is present in 20% to 50% of ATC cases.[5] Other mutations such as NTKR, RET and ALK fusions can be found in less than 2% to 3% of ATC.[5]

Current Management

Treatment Goals

The treatment goal for patients with *BRAF* V600E mutant ATC is to prolong life, delay disease progression, reduce severity of symptoms, minimize AEs, and improve quality of life.

Current Treatment Options

Therapeutic approaches for thyroid cancers include surgery, external beam radiation, and systemic chemotherapy.[6,7] However, these approaches are less effective in ATC, and the response rates to standard systemic therapy are low (< 15%).[6,7] There are no curative options for ATC patients who underwent all aggressive treatment strategies that are currently available.

Pre-clinical murine models suggested that targeted therapy using the combined inhibition of *BRAF* and *MEK* kinases showed promising antitumour activity in *BRAF*-mutated ATC.[8] The combination of *BRAF* and *MEK* inhibition strategy has shown to improve clinical outcomes in *BRAF*-mutated melanoma and lung cancer.[9,10] Since 2018, the US Food and Drug Administration and other countries have approved the combination of *BRAF* kinase inhibitor dabrafenib and the *MEK* inhibitor trametinib for treatment of locally advanced or metastatic *BRAF* V600E mutant ATC based on the initial analysis of a phase II, open-label trial with 16 patients with *BRAF* V600E mutant ATC.[11]

The clinical expert consulted for this review noted that effective therapies with rapid responses are not currently available. Surgery such as thyroidectomy followed by adjuvant radiation with or without chemotherapy is currently used for resectable setting. For unresectable cases, treatment is limited to chemotherapy (e.g., paclitaxel, doxorubicin), which have poor response rates and high toxicity, resulting in poor survival and high symptom burden from the disease.

Information of the drug under review (i.e., dabrafenib and trametinib) is summarized in Table 1.

Unmet Needs and Existing Challenges

There remains therefore an unmet need for more effective therapies that improve overall long-term benefits in this rare disease.

Potential Place in Therapy

Potential Place in Therapy

The clinical experts referred to current guidelines[12,13] suggesting that combination therapy of dabrafenib and trametinib should be used as first-line setting for patients with *BRAF* V600E mutant ATC, as it is a directed therapy, with improved response rates and survival compared to chemotherapy. The clinical experts also suggested that ATC patients should receive prompt diagnosis with molecular testing to confirm *BRAF* mutation, and patients with *BRAF* V600E positive should be immediately transferred to comprehensive cancer centres with expertise in treatment of thyroid cancer, as the disease progresses so rapidly that could result in fatality within days or weeks.

Patient Population

The clinical experts indicated that best suited ATC patients for treatment with combination of dabrafenib and trametinib are those with *BRAF* V600E positive, tested by both immunohistochemistry and confirmed by next-generation sequencing methods. Also, patients should have reasonable performance status, with reasonable co-morbidities that would not be further exacerbated by the therapy.

Assessing the Response to Treatment

The clinical experts explained that response rates assessed by radiological imaging, in addition to improved survival and improvement in symptoms, should be used to determine whether a patient is responding to treatment. Other important clinical endpoints include avoidance or delay of invasive procedures (e.g., tracheostomy), length of hospitalization, and normalization or stabilization of airway and feeding functions.

Discontinuing Treatment

The clinical experts indicated that lack of efficacy, disease progression, and unacceptable toxicity are the main reasons for treatment discontinuation. Some grade 3 and 4 AEs that usually lead to treatment discontinuation include cardiac failure, severe skin toxicities, pancreatitis, and hepatic or renal failure that do not improve despite treatment interruption.

Prescribing Considerations

The clinical experts suggested that patients should be treated at comprehensive cancer centres where diagnosis, molecular testing and established management plan for ATC are available. In addition, treatment can occur in the community setting where close monitoring of toxicities can be conducted in a co-shared care health system model. The combination dabrafenib and trametinib therapy should be prescribed by medical oncologists in a hospital or clinic setting. Specific AEs that should be monitored with this treatment regimen include fevers, chills, skin toxicity, cardiac dysfunction, hyperglycemia, pancreatitis, uveitis, fatigue, nausea, venous thromboembolism, cytopenia, hepatic dysfunction, renal dysfunction, cutaneous malignancies, and fistulation.

Additional Considerations

ATC is a rare condition of thyroid cancer, but very aggressive, and the long-term outcomes remain very poor, with no curative treatment options. The clinical experts mentioned that treatment costs with the combination dabrafenib and trametinib therapy are currently paid by private insurance or by compassionate program offered by Novartis.

CLINICAL REVIEW

Methods

Eligibility Criteria

We conducted a systematic review to identify randomized controlled trial (RCT) or single arm study evidence for dabrafenib plus trametinib for the treatment of patients with *BRAF* V600E mutant ATC. Studies were selected according to the eligibility criteria in Table 2. We also included long-term extension (LTE) studies of included RCTs, indirect treatment comparisons (ITCs) and real-world evidence studies that meet the eligibility criteria.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We selected outcomes (and follow-up times) for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adult patients with *BRAF* V600E mutant ATC with no standard locally or regionally available treatment options
Intervention	Dabrafenib and trametinib administered orally [The proposed regimen would be 150 mg dabrafenib twice daily and 2 mg trametinib once daily until disease progression, intolerable toxicity, or death][a]
Comparator	Best supportive care or no treatment (e.g., single arm studies)
Outcomes	**Efficacy outcomes:** • ORR • DoR • OS • PFS • HRQoL **Safety outcomes:** • Any AEs • Treatment-related AEs • Serious AEs • AEs leading to discontinuation • Death
Study design	RCTs, non-randomized observational studies or single arm studies

AE = adverse events; ATC = anaplastic thyroid cancer; ORR = overall response rate; DoR = duration of response; OS = overall survival; PFS = progression-free survival; HRQoL = Health-related quality of life; RCT = randomized controlled trial.

[a] Based on clinical trial (not from Health Canada indication).

Search Strategy

Detailed methods for literature searches are in the Appendix 1 in the Supplemental Material document.

Study Selection and Data Extraction

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report, with the input from our in-house methodologist.

One reviewer performed data extraction, which was verified by a second reviewer.

Critical Appraisal

Critical appraisal of the included studies was guided by Dows and Black checklist.[14] Table 3 of Appendix 3 in the Supplemental Material document present the strengths and weaknesses of the included studies assessed using the Dows and Black checklist.

Clinical Evidence

Quantity of Research Available

From the search for primary studies, we identified 158 unique references via the searches of databases and registers, of which we excluded 150 by title and abstract. We screened 8 records by full text and included 4 reports of 2 studies.[11,15-17] The list of included studies is presented in Table 1 of Appendix 2 in the Supplemental Material document.

From the search for ITCs, we identified 29 unique records via the searches of databases, of which we did not identify any relevant ITCs.

A list of excluded studies, including reasons for exclusion and a brief report on the clinical outcomes of each study, is in Table 2 of Appendix 2 in the Supplemental Material document.

Systematic Review

Description of Studies

Characteristics of the included studies are summarized in Table 3. Details pertaining to the eligibility criteria, interventions and comparators, and relevant outcome measures are presented in Table 4 of Appendix 4 in the Supplemental Material document.

Table 3: Summary of Included Studies

Study	Population	Intervention and Comparator	Outcomes reported
Subbiah V et al. (2018, 2022, 2023)[11,15,16] Multicentre (41 sites), multicounty, single arm phase II trial	36 patients with *BRAF* V600E mutant ATC Median age 71.0 (range, 47 to 85.0) years; 56% female, 44% male; 50% White, 44% Asian. Most patients had stage IVc (97%). All patients had prior therapy, the majority (83%) received surgery and/or radiation treatment.	**Interventions:** 36 patients received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. **Comparator:** None	Median follow-up: 11.1 months (range, 0.9 to 76.6 months) Primary endpoint: • Investigator-assessed ORR based on RECIST v1.1 Secondary endpoints: • DoR • PFS • OS • Safety
Lorimer et al. (2023)[17]	17 patients diagnosed with advanced ATC that harbour the *BRAF* V600E mutation	**Intervention:** 17 patients received dabrafenib (150 mg twice daily) and	Median follow-up: 12 months (range, 3 to 43 months) • OS

Study	Population	Intervention and Comparator	Outcomes reported
Multicentre (8 sites) retrospective cohort study in UK	Mean age 68 years (SD 9.6 years); 47% female, 53% male. Most patients had stage IVc (65%), followed by stage IVb.	trametinib (2 mg once daily). Median number of treatment cycles was 4.5 (range, 1 to 22 cycles). **Comparator:** None	• PFS • Response rate • Discontinuation rate • Dose reduction rate • Toxicity

ATC = anaplastic thyroid cancer; DoR = duration of response; NA = not applicable; ORR = overall response rate; PFS = progression-free survival; OS = overall survival.

The ROAR Trial

ROAR was a multicentre (41 sites), international (14 countries), single arm, phase II basket study of 8 cohorts of patients with *BRAF* V600E mutated advanced rare cancers (total 206 patients), including ATC.[16]

The ATC cohort comprised 36 patients with unresectable or metastatic ATC who continuously received the combination of dabrafenib 150 mg twice daily capsule and trametinib 2 mg once daily tablet, administered orally, until disease progression, unacceptable toxicity, or death.[15] Dose adjustments were permitted if needed to manage certain toxicities per protocol. It is unknown whether patients had received concomitant treatment or any other rescued treatment in case the disease was worsened.

Eligible patients were adults aged at least 18 years and had histologically or cytologically confirmed, unresectable or metastatic *BRAF* V600E mutant ATC with at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients must have advanced disease and no standard treatment options, Eastern Cooperative Oncology Group (ECOG) performance status of at most 2, ability to swallow and retain orally administered medication, and resolution of any AEs related to previous therapy prior to enrollment.

The primary endpoint was investigator-assessed Objective Response Rate (ORR) per RECIST version 1.1. Secondary endpoints included DoR, PFS, OS, and safety. Table 4 presents the definitions of the outcome measures and the assessed time frame of the outcomes. Given the small sample sizes per histologic cohort, the study employed an adaptive design utilizing a Bayesian hierarchical model that increases the power to detect clinically meaningful differences in the ORR by borrowing information across cohorts while controlling type I error. Briefly, the statistical design borrows information across subgroups with a hierarchical model, such that more borrowing occurs when the groups are consistent (due to similar results), and less borrowing occurs when the groups differ. The hierarchical approach allows the data to drive the amount of borrowing across groups. Details of the statistical analysis can be found in the Data Supplement document of Subbiah V et al. (2018).[11]

Up to 25 patients were enrolled in a primary analysis cohort for each histological subtype, which should be closed early due to efficacy and futility analyses conducted every 12 weeks. Based on efficacy, the ATC primary analysis cohort was recommended for early closure on November 6, 2015, and an expansion cohort was opened. The ATC primary analysis cohort included 15 patients, while an additional 21 patients were enrolled in the expansion cohort. Together, a total of 36 patients comprised the intention-to-treat (ITT) assessable population for efficacy analyses. Data from the expansion cohorts did not contribute to the Bayesian model for the analysis of the primary endpoint, but provided additional efficacy and safety information. All treated patients were included in safety analyses.

Table 4: Description of Outcome Measures in the ROAR Trial

Definition	Time frame
ORR	

Definition	Time frame
The percentage of patients with a tumor response (CR, PR) by investigator assessment as defined by RECIST v1.1 for target lesions and assessed by MRI. • CR is defined as the disappearance of all target lesions; • PR is defined as at least 30% decrease in the sum of the longest diameter of target lesions • OR = CR + PR	Assessed up to 92 months (cut-off date for end of study = December 10, 2021)
DoR	
The time (in weeks or months) from first documented evidence of response (the first response prior to confirmation) until time of documented disease progression or death due to any cause, whichever was first. If the subject did not have a documented date of progression or death, DoR was censored at the date of the last adequate assessment.	Assessed up to 92 months (cut-off date for end of study = December 10, 2021)
PFS	
The interval between the first dose of study treatment and earlier date of first radiologically documented progression or death due to any cause. If the subject did not have a documented date of progression or death, PFS was censored at the date of the last adequate assessment. Progression is defined using RECIST v1.1 criteria, as a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started.	Assessed up to 92 months (cut-off date for end of study = December 10, 2021)
OS	
The time from first dose until death due to any cause. Censoring was performed using the date of last known contact for those who were alive at the time of analysis.	Assessed up to 92 months (cut-off date for end of study = December 10, 2021)

CR = complete response; DoR = duration of response; OR; overall response; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1.

Source: ClinicalTrials.gov (NCT02034110)[18]

The Study by Lorimer et al.

The study by Lorimer et al (2023)[17] was a retrospective chart review study of 8 sites from UK, evaluating the experience on the use of combination therapy dabrafenib and trametinib in patients with confirmed *BRAF* V600E mutant ATC, defined as patients with locally advanced or metastatic ATC with no locoregional, radical treatment options. The authors of the study did not report details of the inclusion and exclusion criteria.

Results

Patient Disposition

The ROAR Trial

From 17 April 2014 to 25 July 2018, a total of 251 patients were screened and 206 patients of 8 cohorts were enrolled in the study, including 36 patients with ATC.[16] Table 5 presents patient disposition of the ROAR trial for ATC cohort. The ATC cohort of 36 patients in the ITT population consisted of 15 patients in the primary analysis cohort and 21 patients from the expansion cohort. Twenty-four patients completed the study, while 12 did not. Reasons for not completed the study included lost of follow up (1 of 12), patient withdrawal (5 of 12), and study terminated by sponsor (6 of 12). Twenty-four of 36 patients died, and 6 of 36 patients remained on study, with 2 patients on going treatment and 4 patients in follow-up.

Table 5: Patient Disposition of the ROAR Trial

Status, n (%)	(N = 36)
Included	36 (100)
Primary analysis cohort	15 (42)
Expansion cohort	21 (58)
Completed	24 (67)
Not completed	12 (33)
Reason not completed	
• Lost of follow up	1 (8)
• Withdrawal by patient	5 (42)
• Study terminated by sponsor	6 (50)
Died	24 (67)
Ongoing	6 (17)
• On treatment	2 (6)
• In follow-up	4 (11)

ATC = anaplastic thyroid cancer.

Source: Subbiah et al. (2022)[15] and Subbiah et al. (2023)[16]

The Study by Lorimer et al.

Nineteen patients with advanced ATC harboring the *BRAF* V600E mutation that were treated with combination of dabrafenib and trametinib were identified. Two patients were excluded from the analysis as 1 patient showed the absence of V600E mutation in further analysis, and 1 patient had rapid disease progression prior to the start of treatment. As a result, 17 patients were included in the final analysis.

Baseline Characteristics

Baseline demographics and disease characteristics of the included studies are presented in Table 6 for the ROAR trial,[15] and Table 7 for the study by Lorimer et al. (2023).[17]

The ROAR Trial

The median age was 71.0 years (range, 47 to 85 years), and more patients were female (56%) than male (44%). A total of 35 out of 36 patients had ATC stage IVc, with a median time since diagnosis of 4.1 months (range, 0.5 to 151.3 months). Most patients had ECOG performance status of 1 (86%). All patients had at least 1 prior therapy, and surgery (83%) or radiotherapy (83%) was common procedure.

Table 6: Baseline Characteristics of Patients in ROAR Trial

Characteristics	(N = 36)
Age, median (range), years	71.0 (47 to 85.0)
Sex , n (%)	
Female	20 (56)
Male	16 (44)
Race, n (%)	
White	18 (50)
Asian	16 (44)
Unknown	2 (6)
ECOG performance status, n (%)	

Characteristics	(N = 36)
0	3 (8)
1	31 (86)
2	2 (6)
BRAF V600E status (central), n (%)	
Confirmed	33 (92)
Not detected	2 (6)
Insufficient quantity	1 (3)
ATC stage	
IV	1 (3)
IVc	35 (97)
TNM staging (primary tumor), n (%)	
T2	1 (3)
T3	3 (8)
T4a	5 (14)
T4b	10 (28)
TX	17 (47)
Time since diagnosis, median (range), months	4.1 (0.5 to 151.3)
Prior radiotherapy regimens	
0	7 (19)
1	18 (50)
2	11 (31)
Prior therapy, n (%)	36 (100)
Surgery	30 (83)
Radiotherapy	30 (83)
Chemotherapy	15 (42)
Radioactive therapy (^{131}I)	11 (31)
Small-molecule targeted therapy	7 (19)
Immunotherapy	4 (11)

ATC = anaplastic thyroid cancer; ECOG = Eastern Cooperative Oncology Group; ^{131}I = radioiodine; TNM = tumor—node—metastases.

Source: Subbiah et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study. *Ann Oncol.* 2022;33(4):406-415. Copyright 2022 by the authors. Available from: https://www.sciencedirect.com/science/article/pii/S0923753422000059?via%3Dihub. Reprinted in accordance with Creative Commons Attribution 4.0 NonCommercial-NoDerivatives International License (CC BY-NC-ND 4.0): https://creativecommons.org/licenses/by-nc-nd/4.0/[15]

The Study by Lorimer et al.

The mean age of 17 patients (8 female and 9 male) was 68 years. Eleven patients had distant metastatic disease (stage IVc), and 6 patients had locally advanced disease. All patients had at least 1 prior therapy, including radiotherapy (100%), surgery (59%), systemic therapy (12%), or radioactive iodine therapy (12%).

Table 7: Baseline Characteristics of Patients in Study by Lorimer et al. (2023)

Characteristics	(N = 17)
Age, mean (SD), years	68 (9.6)
Sex , n (%)	

Characteristics	(N = 17)
Female	8 (47)
Male	9 (53)
Disease stage, n (%)	
IVa	1 (6)
IVb	5 (29)
IVc (distant metastasis)	11 (65)
Prior therapy, n (%)	
Surgery	10 (59)
Systemic therapy	2 (12)
Radioactive therapy (^{131}I)	2 (12)
None	4 (23)
Radiotherapy received	
Adjuvant	7 (47)
Palliative	1 (6)
Radiotherapy (to other sites)	6 (35)

^{131}I = radioiodine; SD = standard deviation.

Source: Reprinted from Clinical Oncology 35, Lorimer C., Cheng L, Chandler R, et al. Dabrafenib and Trametinib Therapy for Advanced Anaplastic thyroid Cancer – Real-world Outcomes from UK Centres, e60 – e66, Copyright (2024), with permission from The Royal College of Radiologists.[17]

Efficacy

The ROAR Trial

Key efficacy results of the ROAR trial are presented in Table 8. They include ORR, DoR, PFS, and OS.

At the data cutoff (14 September 2020), the median follow-up was 11.1 months (range, 0.9 to 76.6 months). Per investigator assessment in the ITT population, the ORR was 56% (20 out of 36 patients), including 3 patients with complete response (CR, 8%), and 17 patients with partial response (PR, 47%). Median investigator-assessed DoR was 14.4 months (95 % CI, 7.4 to 43.6 months). The 12-month and 24-month DoR rates were 50% (95% CI, 27.1 to 69.2%) and 43.7% (21.6 to 64.0%), respectively. Results from the independent radiology assessment of response and DoR were similar with those of the of the investigator assessment.

At the data cutoff, the medians investigator-assessed PFS and OS were 6.7 months (95% CI, 4.7 to 13.8 months) and 14.5 months (95% CI, 6.8 to 23.2 months), respectively. The 12- and 24-month PFS rates were 43.2% (95% CI, 26.6 to 58.8%) and 27.0% (13.2 to 42.9%), respectively. The 12- and 24-month OS rates were 51.7% (33.6 to 67.1%) and 31.5% (16.3 to 47.9%), respectively.

Kaplan-Meier plots for DoR, PFS, and OS are presented in Figure 1, Figure 2 and Figure 3 of Appendix 5 in the Supplemental Material document, respectively.

Table 8: Summary of Key Efficacy Results of the ROAR Trial

Variable	Investigator assessment ITT (N = 36)	Independent radiology assessment ITT (N = 36)
ORR		
Number of patients analyzed	20	19

Variable	Investigator assessment ITT (N = 36)	Independent radiology assessment ITT (N = 36)
% (95% CI)	56 (38.1 to 72.1)	53 (35.5 to 69.6)
CR, n (%)	3 (8)	2 (6)
PR, n (%)	17 (47)	17 (47)
DoR		
Number of patients analyzed	20	20
Median (95% CI), months	14.4 (7.4 to 43.6)	13.6 (3.8 to 39.4)
12-month rates (95% CI), %	50.0 (27.1 to 69.2)	—
24-month rates (95% CI), %	43.7 (21.6 to 64.0)	—
PFS		
Number of patients analyzed	36	36
Median (95% CI), months	6.7 (4.7 to 13.8)	5.5 (3.7 to 12.9)
12-month rates (95% CI), %	43.2 (26.6 to 58.8)	—
24-month rates (95% CI), %	27.0 (13.2 to 42.9)	—
OS		
Number of patients analyzed	36	—
Median (95% CI), months	14.5 (6.8 to 23.2)	—
12-month rates (95% CI), %	51.7 (33.6 to 67.1)	—
24-month rates (95% CI), %	31.5 (16.3 to 47.9)	—

CI = confidence interval; CR = complete response; DoR = duration of response; ITT = intention-to-treat; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response.

Source: Subbiah et al (2022)[15] and Subbiah et al (2023)[16]

The Study by Lorimer et al.

The key efficacy results of the study by Lorimer et al. (2023)[17] are presented in Table 9. These are ORR, OS and PFS.

The median duration of follow-up was 12 months (range, 3 to 43 months). Two patients (12%) had complete radiological responses, and 12 patients (71%) had partial responses, leading to the ORR of 82%. The median OS was 6.9 months (95% CI, 2.5 months to not reached). The median PFS was 4.7 months (95% CI, 1.4 to 7.8 months). Ten patients died by the time of censoring.

Kaplan-Meier plots for OS and PFS are presented in Figure 4, Figure 5 of Appendix 5 in the Supplemental Material document.

Table 9: Summary of Key Efficacy Results of the Study by Lorimer at al.

Variable	(N = 17)
ORR, n (%)	14 (82)
CR, n (%)	2 (12)
PR, n (%)	12 (71)
Median OS (95% CI), months	6.9 (2.5 to NR)
Median PFS (95% CI), months	4.7 (1.4 to 7.8)

CI = confidence interval; CR = complete response; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response.

Source: Lorimer et al. (2023)[17]

Although HRQoL outcomes were considered important to this review, they were not assessed in the included studies.

Safety

The ROAR Trial

Detailed results for safety outcomes for the ROAR trial[15,16] are presented in Tables 5 to 11 in Appendix 6 in the Supplemental Material document.

All patients experienced at least 1 AE, of which 27 patients (75%) experienced AEs related to treatment. The most frequent AEs of any grade were pyrexia (n = 17, 47%), anemia (n = 13, 36%), decreased appetite (n = 12, 33%), fatigue (n = 12, 33%), and nausea (n = 12, 33%).

Twenty patients (56%) experienced serious AEs, of which 7 (19%) were suspected to be related to the study treatment, and 3 (8%) died due to serious AEs. Reported serious AEs of more than 1 patients were pneumonia (n = 8, 22%), pleural effusion (n = 3, 8%), urinary tract infection (n = 2, 6%), decreased neutrophil count (n = 2, 6%), hematochezia (n = 2, 6%), and leukopenia (n = 2, 6%). Serious AEs suspected to be related to the study treatment included pyrexia (n = 1, 3%), decreased neutrophil count (n = 2, 6%), and leukopenia (n = 2, 6%).

Twenty-four patients (67%) died, with the most common primary causes of death was disease progression in 20 patients (56%).

The median duration of exposure to both dabrafenib and trametinib was 7.0 months (range, 1 to 63 months). One of the main reasons for study treatment discontinuation was disease progression (n = 22, 61%). Six patients (17%) had AEs that led to permanent discontinuation of study treatment. AEs leading to discontinuation of study treatment in more than 1 patient were dyspnea (n = 2, 6%) and pleural effusion (n = 2, 6%).

A total of 18 patients (50%) and 17 patients (47%) had AEs requiring dose interruption and dose reduction, respectively. Pyrexia (n = 5, 14%) and pneumonia (n = 3, 8%) were the most frequent AEs requiring dose interruption. Pyrexia (n = 6, 17%) was also the most common AE leading to dose reduction.

The Study by Lorimer et al.

Detailed results for safety outcomes for the study by Lorimer et al. (2023)[17] are presented in Tables 12 to 14 in Appendix 6 in the Supplemental Material document.

Most of the AEs were of grade 1 and 2. Common grade 1 AEs in more than 1 patient were breathlessness (n = 5, 30%), decreased appetite (n = 4, 24%), fatigue (n = 4, 24%), oral mucositis (n = 4, 24%), low mood (n = 3, 18%), nausea (n = 2, 12%), skin dryness (n = 2, 12%), diarrhea (n = 2, 12%), musculoskeletal pain (n = 2, 12%), and constipation (n = 2, 12%). Common grade 2 AEs in more than 1 patient were fever (n = 4, 24%), breathlessness (n = 2, 12%), fatigue (n = 2, 12%), nausea (n = 2, 12%), skin dryness (n = 2, 12%), and eye symptoms (n = 2, 12%).

Treatment was temporarily interrupted in 11 patients (65%), including pause due to surgery (n = 3, 18%), and fever (n = 3, 18%). Nine patients (53%) had AEs requiring dose reduction. Reasons for dose reduction of dabrafenib were nausea and uveitis (n = 1, 6%), pneumonia and fatigue (n = 1, 6%), fever (n = 2, 12%), anemia (n = 1, 6%), and fever and nausea (n = 1, 6%). Reasons for dose reduction of trametinib were cramps (n = 1, 6%), anemia (n = 1, 6%), and poor appetite (n = 1, 6%).

Critical Appraisal

Internal Validity

The ROAR trial[15] was a nonrandomized, single arm, open-label trial. Such single arm trials have been used to assess the clinical efficacy and safety of anticancer drugs for rare disease to support regulatory approval.[19] This type of small open-label, and non-controlled study design would have led the causal inference of treatment effect from study drug impossible (i.e., to what extent that the observed OS in terms of a median survival of 14.5 months and 24-month survival rate of 31.5% could entirely be attributable to the use of study drug). Anecdotal observation may suggest that if without the study treatment, the patients' median survival would be much shorter. Similar arguments apply to all other study endpoints in the trial. However, such benefit could not be exactly estimated.

The small sample size may render a limited assessment of AEs, especially those infrequent but severe AEs. This further compromised our over assessment and conclusion, for instance, that the benefits if established outweigh the potential harms.

Additional limitations may include the lack of assessment of patient important outcomes, such as HRQoL, function and symptoms as well as outcomes of disease burdens, such as avoidance or delay of disease procedures, and duration of hospital stay, etc.

The clinical experts noted that it is not feasible to conduct an RCT on rare and extremely aggressive disease such as ATC, which has no other effective therapeutic options.

External Validity

The ROAR trial[15] had strict eligibility criteria, which permitted only patients having good baseline performance status and fitness (i.e., ECOG PS of 0 to 2, mostly 1), ability to swallow orally administered medication, and adequate organ function. These factors of the ROAR population may limit the generalizability to the real-world population of ATC, in which patients may not be able to swallow or have poor performance status. The clinical experts noted that liquid formulations of the medications are available that can be administered through nasogastric tube in patients who could not swallow.

BRAF/MEK targeted therapy using the combination of dabrafenib and trametinib has been considered as first-line treatment for *BRAF* V600E mutant ATC since FDA approval in 2018.[12,13] The trial regimen and the requirement of significant expertise across multiple medical disciplines including genetic testing can be generalizable to the clinical setting in Canada, whose healthcare system can handle great demands for the management of *BRAF*-mutated ATC.

The study by Lorimer et al. (2023)[17] was a retrospective, single arm, chart review study, which provided real-world data on dabrafenib and trametinib therapy for advanced ATC. The study had similar limitations in both internal and external validity as the ROAR trial. In addition, real world evidence studies can have several limitations including risk of biases (e.g., information, recall and detection), low internal validity, and lack of quality control surrounding data collection. Indeed, details on measurements of radiological assessments were not collected and independent pathology reviews were not conducted in the study by Lorimer et al. (2023).[17]

Discussion

Efficacy

This review included a phase II, nonrandomized, single arm, open-label (ROAR) trial[11,15,16] and a retrospective single arm chart review study by Lorimer et al. (2023).[17] Both studies reported the efficacy and safety dabrafenib and trametinib combination therapy in *BRAF* V600E mutant ATC.

The ROAR trial[15] demonstrated an investigator-assessed ORR of 56%, including 3 CRs and 17 PRs. Median duration PFS and OS were 6.7 months, and 14.5 months, respectively. The 12-month DoR, PFS and OS rates of 50%, 43.2%, and 51.7%, respectively. The study by Lorimer et al (2023)[17] reported higher ORR of 82%, with shorter survival (median PFS and OS of 4.7 months and 6.9 months, respectively) compared to the ROAR trial. The difference between outcomes reported in the two included studies may stem from high heterogeneity in patient selection in the real world, while stricter eligibility criteria were applied in the ROAR trial, with patients having a better baseline performance status. However, the clinical experts noted that response rates are more important outcomes than OS or PFS, particularly for a rare and deadly disease such as ATC.

In this review, we excluded 4 studies including 1 case series[20] and 3 retrospective studies[21-23] for various reasons. Table 2 of Appendix 2 in the Supplemental Material document presents reasons for exclusion. It also provides a summary of clinical outcomes of those studies focussing on the combination dabrafenib and trametinib therapy for *BRAF* V600E mutant ATC as additionally interested information. Briefly, 2 studies[20,21] reported ORR of around 80%, 3 studies[21-23] reported median OS values varied from 10 to 12 months, 1 study[22] reported 12-month OS rate of 71%, and 2 studies[21,22] reported median PFS of 7 and 9 months. These results may add further evidence for the potential benefit of the combination dabrafenib and trametinib therapy in the treatment of *BRAF* V600E mutant ATC.

Despite the successful increase in responses and survival with the combination dabrafenib and trametinib therapy compared to previous treatments, resistance (both initial and acquired) to treatment remains a challenge in patients with *BRAF* V600E mutant ATC. At the time of analysis, 24 of 36 patients (67%) in the ROAR trial,[15,16] and 12 of 17 patients (71%) in the study by Lorimer et al. (2023)[17] had disease progression on treatment, highlighting the need for other treatment options for more durable responses.

Indeed, the clinical experts indicated that this combination therapy is not a cure for the disease, but the goal of treatment is to prolong survival, delay disease progression, reduce severity of symptoms, minimize AEs, and improve quality of life. Additional goals of this therapy include reduced hospitalization, maintaining current ECOG performance status, and delay certain procedures such as mechanical ventilation and intubation. The clinical experts also noted that currently there are no other treatment options for patients who fail dabrafenib and trametinib combination therapy.

Harms

One of the most common AEs of dabrafenib plus trametinib treatment was pyrexia, which could be resolved by dose interruption or dose reduction. Other frequent AEs included anemia, decreased appetite, fatigue, nausea. The clinical experts indicated that specific AEs should be monitored with this treatment regimen including fevers, chills, skin toxicity, cardiac dysfunction, hyperglycemia, pancreatitis, uveitis, fatigue, nausea, venous thromboembolism, cytopenia, hepatic dysfunction, renal dysfunction, cutaneous malignancies, and fistulation. The authors of the ROAR trial noted that overall safety profile of dabrafenib plus trametinib for treatment of *BRAF* V600E mutated ATC was manageable and consistent with the findings in previous reports for other indications, such as melanoma[9] and non-small-cell lung cancer.[10]

Conclusion

The evidence from the phase II ROAR basket study[11,15,16] and the study by Lorimer et al (2023)[17] suggests that *BRAF* V600E mutant ATC patients with a reasonable performance status can be effectively treated with dabrafenib plus trametinib. The combination therapy increased responses and improved survival with manageable toxicities. However, the benefits and harms of the intervention remain uncertain due to small sample sizes and the study design of the included studies. The uncertainty of the clinical evidence stems from the difficulty of conducting randomized clinical trials in rare and aggressive diseases like ATC where effective treatments are currently not available. In addition, disease progression and mortality rate remain high, suggesting that targeted therapy with dabrafenib plus trametinib remains a challenge. Timely access to multidisciplinary and specialized health care, high-complexity diagnostic including molecular testing, and development of novel targeted therapies would provide hope to transition of such life-threatening disease without treatment options into a potentially manageable condition. Despite the uncertainties of the clinical evidence presented in this review, the clinical experts remain confident that the combination therapy of dabrafenib and trametinib should be prescribed to patients diagnosed with locally advanced or metastatic *BRAF* V600E-mutated ATC without delay.

Economic Review

The economic review consisted of a cost comparison for dabrafenib plus trametinib for adult patients with BRAF V600E anaplastic thyroid cancer with no standard locally or regionally available treatment options. No comparators were identified for the population of interest.

Based on public list prices, dabrafenib plus trametinib is expected to have a per patient cost of $18,018 per 28 days (Table 1). As there are no identified comparators that may be displaced by the regimen, the reimbursement of dabrafenib plus trametinib for the treatment of adults with BRAF V600E ATC is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- Evidence from the phase II single arm ROAR basket study[11,15,16] and the retrospective chart review study by Lorimer et al,[17] suggests that patients with BRAF V600E ATC with reasonable performance status may experience increased responses and improved survival with manageable toxicity relative to no active treatment.
- The patent for trametinib is expected to expire mid-2025.[24] As such, it is possible that 1 or more generic versions of trametinib may become available. If so, the daily and 28-day cost of the dabrafenib plus trametinib regimen would be less than estimated in this review. The earliest patent for dabrafenib is set to expire in 2029.
- While testing for BRAF V600 mutations is standardly available in some jurisdictions (e.g., Ontario), this may not be the case in all jurisdictions. In jurisdictions which do not currently fund testing, the reimbursement of dabrafenib plus trametinib would also be associated with the cost of additional testing.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on November 5, 2024.

Conclusion

The reimbursement of dabrafenib plus trametinib for the treatment of adult patients with BRAF V600E ATC is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, dabrafenib plus trametinib may increase response and improve survival with manageable toxicities relative to no active treatment.

Given that dabrafenib plus trametinib is associated with increased drug acquisition costs and likely but uncertain clinical benefit relative to no active treatment, the reimbursement of dabrafenib plus trametinib will add costs to the public health care system with uncertain benefit.

References

1. Ragazzi M, Ciarrocchi A, Sancisi V, Gandolfi G, Bisagni A, Piana S. Update on anaplastic thyroid carcinoma: morphological, molecular, and genetic features of the most aggressive thyroid cancer. *Int J Endocrinol*. 2014;2014:790834. doi:10.1155/2014/790834
2. Shaw A, Semenciw R, Mery L. Cancer in Canada fact sheet series #1 - thyroid cancer in Canada. *Chronic Dis Inj Can*. 2014;34(1):64-8. Accessed November 20, 2024. https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/hpcdp-pspmc/34-1/assets/pdf/CDIC_MCC_Vol34_1_9_Shaw_E.pdf
3. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin Oncol (R Coll Radiol)*. 2010;22(6):486-97. doi:10.1016/j.clon.2010.03.013
4. Cleveland Clinic. Anaplastic Thyroid Cancer (ATC). 2022. Accessed November 20, 2024. https://my.clevelandclinic.org/health/diseases/23539-anaplastic-thyroid-cancer-atc
5. Califano I, Smulever A, Jerkovich F, Pitoia F. Advances in the management of anaplastic thyroid carcinoma: transforming a life-threatening condition into a potentially treatable disease. *Rev Endocr Metab Disord*. 2024;25(1):123-147. doi:10.1007/s11154-023-09833-1
6. Saini S, Tulla K, Maker AV, Burman KD, Prabhakar BS. Therapeutic advances in anaplastic thyroid cancer: a current perspective. *Mol Cancer*. 2018;17(1):154. doi:10.1186/s12943-018-0903-0
7. Fagin JA, Wells SA, Jr. Biologic and Clinical Perspectives on Thyroid Cancer. *N Engl J Med*. 2016;375(11):1054-67. doi:10.1056/NEJMra1501993
8. McFadden DG, Vernon A, Santiago PM, et al. p53 constrains progression to anaplastic thyroid carcinoma in a Braf-mutant mouse model of papillary thyroid cancer. *Proc Natl Acad Sci U S A*. 2014;111(16):E1600-9. doi:10.1073/pnas.1404357111
9. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367(18):1694-703. doi:10.1056/NEJMoa1210093
10. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993. doi:10.1016/s1470-2045(16)30146-2
11. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. *J Clin Oncol*. 2018;36(1):7-13. doi:10.1200/JCO.2017.73.6785
12. Filetti S, Durante C, Hartl D, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(12):1856-1883. doi:10.1093/annonc/mdz400
13. Haddad RI, Bischoff L, Ball D, et al. Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(8):925-951. doi:10.6004/jnccn.2022.0040
14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-84. doi:10.1136/jech.52.6.377
15. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study. *Ann Oncol*. 2022;33(4):406-415. doi:10.1016/j.annonc.2021.12.014
16. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med*. 2023;29(5):1103-1112. doi:10.1038/s41591-023-02321-8
17. Lorimer C, Cheng L, Chandler R, et al. Dabrafenib and Trametinib Therapy for Advanced Anaplastic Thyroid Cancer - Real-World Outcomes From UK Centres. *Clin Oncol (R Coll Radiol)*. 2023;35(1):e60-e66. doi:10.1016/j.clon.2022.10.017
18. Novartis Pharmaceuticals. *NCT02034110: Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects With BRAF V600E-Mutated Rare Cancers*. ClinicalTrials.gov; 2023. Accessed February 18, 2025. https://clinicaltrials.gov/study/NCT02034110
19. Agrawal S, Arora S, Amiri-Kordestani L, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. *JAMA Oncol*. 2023;9(2):266-272. doi:10.1001/jamaoncol.2022.5985
20. Bueno F, Smulever A, Califano I, et al. Dabrafenib plus trametinib treatment in patients with anaplastic thyroid carcinoma: an Argentinian experience. *Endocrine*. 2023;80(1):134-141. doi:10.1007/s12020-022-03295-2
21. Chang CF, Yang MH, Lee JH, et al. The impact of BRAF targeting agents in advanced anaplastic thyroid cancer: a multi-institutional retrospective study in Taiwan. *Am J Cancer Res*. 2022;12(11):5342-5350. Accessed October 30, 2024. https://e-century.us/files/ajcr/12/11/ajcr0146297.pdf
22. da Silva TN, Rodrigues R, Saramago A, et al. Target therapy for BRAF mutated anaplastic thyroid cancer: a clinical and molecular study. *Eur J Endocrinol*. 2023;188(1):10. doi:10.1093/ejendo/lvac011
23. Gupta MK, Misariu AM, Saydy N, et al. A Multicentre Retrospective Study of Anaplastic Thyroid Cancer in the Era of Targeted Therapy in a Public Health Care System: Canada's Experience. *Thyroid*. 2023;33(11):1374-1377. doi:10.1089/thy.2023.0088
24. Health Canada. Patent Register. 2025. Accessed January 20, 2025. https://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp