CDA-AMC Reimbursement Review

Supplemental Material

DABRAFENIB PLUS TRAMETINIB

(Non-Sponsored Review)

Therapeutic area: *BRAF* V600E-mutant anaplastic thyroid cancer

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Appendix 1: Methods

Clinical Literature Search

Methods

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were dabrafenib, trametinib, and thyroid cancer. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial searches were completed on October 30, 2024. Regular alerts updated the searches until the meeting of the Formulary Management Expert Committee meeting on March 20, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials.

A focused literature search for indirect treatment comparisons (ITCs) dealing with dabrafenib and trametinib or anaplastic thyroid cancer was run in MEDLINE on October 29, 2024. Retrieval was not limited by publication date or by language.

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: October 30, 2024

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading

Syntax	Description
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy
Embase <1974 to 2024 October 29>
Ovid MEDLINE(R) ALL <1946 to October 29, 2024>

1 (dabrafenib* or Tafinlar* or Rafinlar* or Taffiner* or Tafinra* or Finlee* or drb436 or drb-436 or gsk-2118436* or gsk2118436* or QGP4HA4G1B).ti,ab,kf,ot,hw,rn,nm.
2 (trametinib* or Mekinist* or Megsel* or Meqsel* or Mekinst* or Spexotras* or gsk-1120212* or gsk1120212* or jtp-74057 or jtp74057 or snr-1611 or snr1611 or tmt-212 or tmt212 or 33E86K87QN).ti,ab,kf,ot,hw,rn,nm.
3 1 and 2
4 Thyroid Neoplasms/ or Thyroid Carcinoma, Anaplastic/
5 (thyroid* and (cancer* or neoplasm* or carcinoma* or tumo?r* or BRAF V600E or BRAFV600E)).ti,ab,kf.
6 4 or 5
7 3 and 6

8 7 use medall
9 *dabrafenib/
10 (dabrafenib* or Tafinlar* or Rafinlar* or Taffiner* or Tafinra* or Finlee* or drb436 or drb-436 or gsk-2118436* or gsk2118436*).ti,ab,kf,dq.
11 9 or 10
12 *trametinib/
13 (trametinib* or Mekinist* or Megsel* or Meqsel* or Mekinst* or Spexotras* or gsk-1120212* or gsk1120212* or jtp-74057 or jtp74057 or snr-1611 or snr1611 or tmt-212 or tmt212).ti,ab,kf,dq.
14 12 or 13
15 11 and 14
16 anaplastic thyroid carcinoma/ or thyroid cancer/ or thyroid carcinoma/
17 (thyroid* and (cancer* or neoplasm* or carcinoma* or tumo?r* or BRAF V600E or BRAFV600E)).ti,ab,kf.
18 16 or 17
19 15 and 18
20 19 not (conference abstract or conference review).pt.
21 20 use oemezd
22 8 or 21
23 remove duplicates from 22

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.
[Search -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR "drb-436" OR "gsk-2118436" OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR "gsk-1120212" OR gsk1120212 OR "jtp-74057" OR jtp74057 OR "snr-1611" OR snr1611 OR "tmt-212" OR tmt212) AND thyroid]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
[Search terms -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR "drb-436" OR "gsk-2118436" OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR "gsk-1120212" OR gsk1120212 OR "jtp-74057" OR jtp74057 OR "snr-1611" OR snr1611 OR "tmt-212" OR tmt212) AND thyroid]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.
[Search terms -- Dabrafenib, tafinlar, trametinib, mekinist, finlee, anaplastic]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR "drb-436" OR "gsk-2118436" OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR "gsk-1120212" OR gsk1120212 OR "jtp-74057" OR jtp74057 OR "snr-1611" OR snr1611 OR "tmt-212" OR tmt212) AND thyroid]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- Dabrafenib, tafinlar, trametinib, mekinist, finlee, anaplastic]

Grey Literature

Search dates: October 22-24, 2024

Keywords: thyroid, dabrafenib, Tafinlar, Finlee, trametinib, Mekinist

Limits: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies

- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 2: Included and Excluded Studies

Table 1: Included Studies

Reference	Study Design and Description
Subbiah V, Kreitman RJ, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018 Jan 1;36(1): 7-13.	Open-label, nonrandomized, phase II basket study This paper reported the interim analysis of 15 patients with *BRAF* V600E mutant ATC
Subbiah V, Kreitman RJ, 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 Apr;33(4): 406-415.	As above This paper reported the updated data from continued followed-up of the ROAR ATC cohort of total 36 patients.
Subbiah V, Kreitman RJ, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. Nat Med. 2023 May;29(5): 1103-1112.	As above This paper reported the final results of the ROAR study for all cancer cohorts, including ATC.
Lorimer C, Cheng L, et al. Dabrafenib and Trametinib Therapy for Advanced Anaplastic Thyroid Cancer - Real-World Outcomes From UK Centres. Clin Oncol (R Coll Radiol). 2023 Jan;35(1): e60-e66.	Retrospective chart review study This paper reported the real-world data on the use of combination dabrafenib and trametinib therapy in 17 patients with *BRAF* V600E mutant ATC.

ATC = anaplastic thyroid cancer.

Table 2: Excluded Studies

Study	Reason for Exclusion & Outcomes of ATC Cases Treated with Dabrafenib and Trametinib
Bueno F, Smulever A, et al. Dabrafenib plus trametinib treatment in patients with anaplastic thyroid carcinoma: an Argentinian experience. Endocrine. 2023 Apr;80(1):134-141.	Case series with 5 patients ORR = 80% (2 CR; 2 PR) Median DoR = 20 weeks (range, 16 to 92 weeks) Mortality: 3 patients (60%) died at 20 weeks of follow-up OS and PFS were not reached due to lack of events.
Chang C-F, Yang M-H, 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 Nov 15;12(11):5342-5350.	Retrospective cohort study with unclear comparator 11 ATC patients received combination treatment with dabrafenib and trametinib had *BRAF* V600E mutation, while 33 ATC patients who did not received combination therapy were unclear if they all possessed *BRAF* mutation. Median OS = 10.4 months (95% CI, 1.6 to 19.3) Median PFS = 7.4 months (95% CI, 1.6 to 13.1 months) ORR = 81.8% (1 CR; 8 PR)
Da Silva TN, Rodrigues R, et al. Target therapy for BRAF mutated anaplastic thyroid cancer: a clinical and molecular study. Eur J Endocrinol. 2023 Jan 10;188(1):lvac011.	Retrospective cohort study with irrelevant comparator 9 ATC patients with *BRAF* V600E mutation who were treated with dabrafenib and trametinib were compared with 8 patients with BRAF wild type under multimodal therapy, and with 10 patients with BRAF wild type under compassionate care. Median follow-up = 530 days Median OS = 475 days 12-month OS = 71%

Study	Reason for Exclusion & Outcomes of ATC Cases Treated with Dabrafenib and Trametinib
	Median PFS = 270 days 12-month PFS = 43% 30-day ORR: 7 patients 90-day ORR: 7 patients Alive at end of follow-up: 5 patients
Gupta MK, Misariu A-M, 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 Nov;33(11):1374-1377.	Letter to Editor Mixed intervention. Of 27 ATC patients with *BRAF* V600E receiving targeted therapy, 21 received combination dabrafenib and trametinib, and 6 received lenvatinib only. 2-year OS: Adjusted HR = 0.52 (95% CI, 0.31 to 0.87; P = 0.014) Median OS = 12.1 months

ATC = anaplastic thyroid cancer; CI = confidence interval; CR = complete response; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response.

Appendix 3: Critical Appraisal of Included Publication

Table 3: Strengths and Weaknesses of Clinical Studies Using the Downs and Black Checklist

Strengths	Weaknesses
ROAR trial[2,3]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • The authors of the study reported the inclusion and exclusion criteria for the study population. • Safety outcomes of the intervention were reported. • Actual probability values were reported for the main outcomes. **External validity:** • The study was a multinational, multicentre trial. • The study was conducted in hospital setting, where all patients with cancer were treated. • Patients who participated in the study appeared to be representative of the entire population from which they were recruited. **Internal validity – bias:** • Statistical analyses including the 95% CIs were used appropriately, and the main outcome measures such as ORR, PFS and OS were prespecified. • Missing data were not reported. All patients who received the study treatment per protocol were completed in the following up of outcomes.	**Internal validity – bias:** • The study was single-arm, open-label trial, therefore, lacking an appropriate control arm would render it difficult in making causal inference on the efficacy of treatment. • As ATC is a rare disease, sample size may lead to imprecision in effect estimates due to difficulty in recruitment of patients.
Lorimer et al. (2023)[4]	
Reporting:	**Reporting:**

• The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the treatment of interest, and the main findings were clearly described. • Safety outcomes of the intervention were reported. • Actual probability values were reported for the main outcomes. **External validity:** • The study was a multicentre retrospective cohort study from UK. • The study was conducted in hospital setting, where all patients with cancer were treated. **Internal validity – bias:** • The study outcomes and treatments were clearly defined and reviewed.	• The authors of the study did not report the inclusion and exclusion criteria for the study population. **External validity:** • Patients might not be representative of the entire population due to highly selective cohort with extremely small sample size. **Internal validity – bias:** • The study was a retrospective chart review of existing database from 8 sites in UK. Lack of appropriate control making it difficult to draw any causal conclusion.

Appendix 4: Characteristics of Included Publication

Table 4: Characteristics of Included Studies

Study details	Population	Intervention and Comparator	Study outcomes
Subbiah V et al. (2018, 2022, 2023) [2,3] **Study name:** Rare Oncology Agnostic Research (ROAR) **Study design:** Multicentre (41 sites), single arm, phase II basket study of 8 cohorts of patients with *BRAF* V600E mutated advanced rare cancers. **Countries:** USA (8 sites), Austria (4 sites), Belgium (1 site), Canada (1 site), Denmark (1 site), France (6 sites), Germany (5 sites), Italy (3 sites), Japan (2 sites), Republic of Korea (2 sites), Netherlands (4 sites), Norway (1 site), Spain (2 sites), Sweeden (1 site). **Objective:** To determine the efficacy and safety of oral dabrafenib in combination with oral trametinib in 9 cohorts of patients with rare cancers harboring the *BRAF* V600E mutation, including ATC cohort of 36 patients. The study by Subbiah V et al. (2018)[2] reported the results for the 16 ATC patients only. The study by Subbiah V et al. (2022)[3] reported an updated analysis of the efficacy and safety of dabrafenib plus trametinib in the full ROAR ATC cohort of 36 patients. The study by Subbiah V et al. (2023)[3] reported the results of 206 patients with BRAF V600E mutated rare cancers	This study reported the results of 36 ATC patients. **Inclusion criteria:** • 18 years or more • Advanced disease and no standard locally or regionally available treatment options[a] • Confirmed *BRAF* V600E mutation • ECOG performance status of 0 to 2 • Ability to swallow orally administered medication • Adequate organ function **Exclusion criteria:** • Prior treatment with BRAF and/or MEK inhibitor(s) • History of malignancy with confirmed activating RAS mutation at any time. • Radiotherapy was not permitted within 7 days. • Any treatment-related AEs must have been resolved before enrollment. • Patients with ATC who were potentially curable by surgical excision alone, had not received standard-of-care treatment, or had thyroid lymphoma, sarcoma, or metastatic disease from other sites were also excluded.	**Intervention:** Patients received continuous dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) given orally 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[b] based on RECIST v1.1 Secondary endpoints: • DoR[c] • PFS[d] • OS[e] • Safety

Study details	Population	Intervention and Comparator	Study outcomes
in 8 cohorts, including 36 patients with ATC.			
Lorimer et al. (2023)[4] **Study name:** NA **Study design:** Multicentre (8 sites) retrospective chart review study **Country:** UK **Objective:** To retrospectively evaluate the use of combination therapy of dabrafenib and trametinib in patients with *BRAF* V600E mutant ATC	Patients with confirmed *BRAF* V600E mutant ATC, with no locoregional, radical treatment options **Inclusion criteria:** NR **Exclusion criteria:** NR	**Intervention:** 17 patients with *BRAF* V600E mutation received dabrafenib and trametinib treatment. **Comparator:** None	Median follow-up: 12 months (range, 3 to 43 months) • OS • PFS • Response rate • Discontinuation rate • Dose reduction rate • Toxicity

ATC = anaplastic thyroid cancer; DoR = duration of response; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SD = stable disease.

[a] Determined by treating physician, measurable disease on the basis of Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1

[b] Defined as proportion of patients with tumor response (complete response [CR], partial response [PR]) by investigator assessment as defined by Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1). Per RECIST v1.1 for target lesions and assessed by MRI: CR = Disappearance of all target lesions; PR = >=30% decrease in the sum of the longest diameter of target lesions; ORR = CR + PR.

[c] Defined as the time from the first documented evidence for CR or PR until documented disease progression or death from any cause.

[d] Defined as the time from the first dose to disease progression or death.

[e] Defined as the time from the first dose of the study drug until death from any cause.

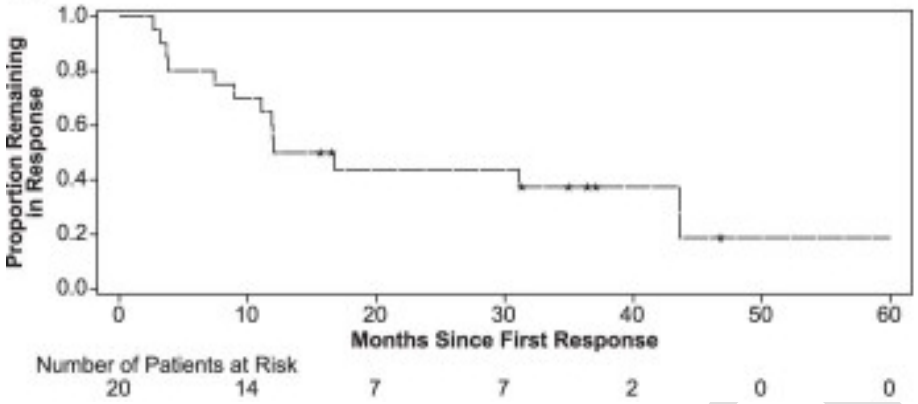
[f] Defined as the time from the date of receiving dabrafenib and trametinib to the date of death or disease progression.

[g] Defined as the time from the date of diagnosis to the death of death or last following-up.

Source: Subbiah et al. (2022)[3] and ClinicalTrials.gov (NCT02034110)[5]

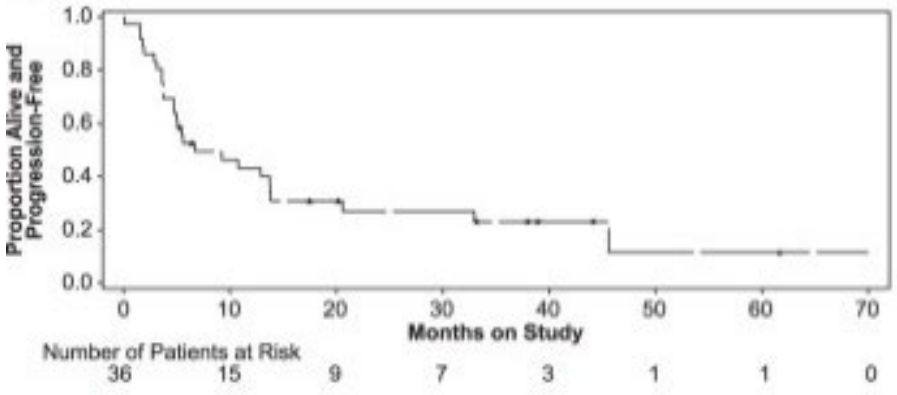
Appendix 5: Kaplan-Meier Plots for Study Endpoints

Figure 1: Duration of Response in the ROAR Trial



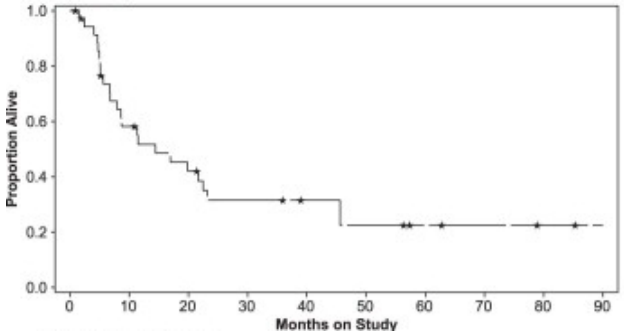
Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Figure 2: Progression Free Survival in the ROAR Trial



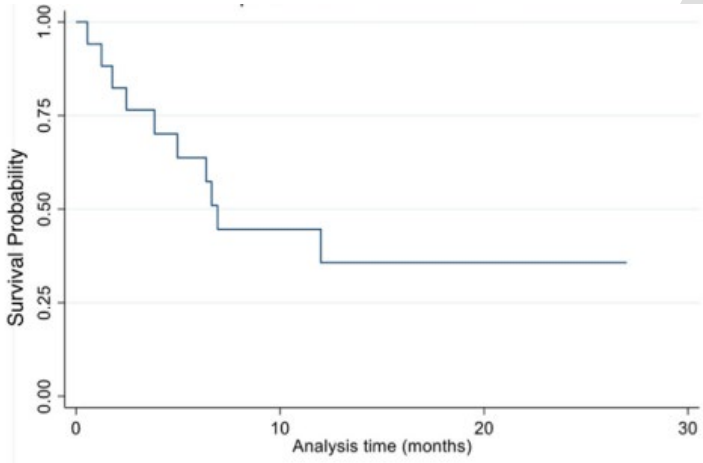
Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Figure 3: Overall Survival in the ROAR Trial



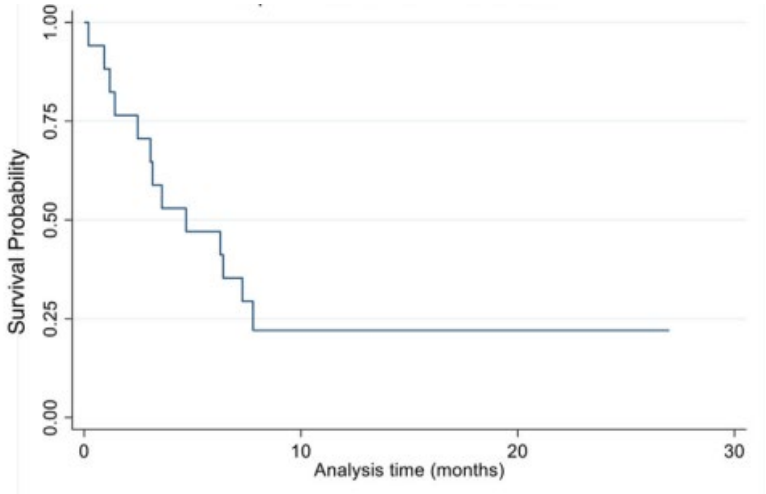
Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Figure 4: Overall Survival in the Study by Lorimer et al.



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.[4]

Figure 5: Progression Free Survival in the Study by Lorimer et al.



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.[4]

Appendix 6: Summary of Safety Outcomes

Table 5: Summary of Safety in the ROAR trial

Category, n (%)	(N = 36)
Any AEs	36 (100)
Treatment related	27 (75)
AEs leading to discontinuation of study treatment	6 (17)
AEs leading to dose reduction	17 (47)
AEs leading to dose interruption	18 (50)
Serious AEs	20 (56)
Treatment related serious AEs	7 (19)
Fatal	3 (8)
Treatment related	0 (0)

AE = adverse event.

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-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0): https://creativecommons.org/licenses/by-nc-nd/4.0/ [3]

Table 6: Most Frequent AEs by Preferred Terms in the ROAR Trial

Preferred term	(N = 36) Any Grade n (%)	(N = 36) Grade 3 or 4 n (%)
Any AEs	36 (100)	21 (58)
Pyrexia	17 (47)	0 (0)
Anemia	13 (36)	7 (19)
Decreased appetite	12 (33)	1 (3)
Fatigue	12 (33)	3 (8)
Nausea	12 (33)	0 (0)
Rash	10 (28)	0 (0)
Dyspnea	9 (25)	1 (3)
Pneumonia	9 (25)	7 (19)
Chills	8 (22)	0 (0)
Constipation	8 (22)	0 (0)
Dizziness	8 (22)	1 (3)
Hyponatremia	8 (22)	6 (17)
Diarrhea	7 (19)	1 (3)
Headache	7 (19)	0 (0)
Hypoalbuminemia	7 (19)	2 (6)
Blood AP increased	6 (17)	2 (6)
Dysphagia	6 (17)	0 (0)
Hypotension	6 (17)	2 (6)
Vomiting	6 (17)	0 (0)

AE = adverse event; ATC = anaplastic thyroid cancer; AP = alkaline phosphatase.

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-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0): https://creativecommons.org/licenses/by-nc-nd/4.0/ [3]

Table 7: Serious AEs in the ROAR Trial

Preferred term	(N = 36) n (%)
Any event	20 (56)
Pneumonia	8 (22)
Pleural effusion	3 (8)
Urinary tract infection	2 (6)
Acute kidney injury	2 (6)
Neutrophil count decreased	2 (6)
Hematochezia	2 (6)
Leukopenia	2 (6)
Pyrexia	1 (3)
Sepsis	1 (3)
Dehydration	1 (3)
Fatigue	1 (3)
Pulmonary embolism	1 (3)
Anemia	1 (3)
Ejection fraction decreased	1 (3)
Femoral neck fracture	1 (3)
Hematuria	1 (3)
Hypotension	1 (3)
Neutropenia	1 (3)
Wound infection	1 (3)
Aortic thrombosis	1 (3)
Autoimmune hemolytic anemia	1 (3)
Bladder transitional cell carcinoma	1 (3)
Cardiac ventricular thrombosis	1 (3)
Clavicle fracture	1 (3)
Clostridium difficile infection	1 (3)
Diverticulitis	1 (3)
Dizziness	1 (3)
Dysphagia	1 (3)
Dyspnea	1 (3)
Facial nerve disorder	1 (3)
Hallucination	1 (3)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (3)
Hyponatremia	1 (3)
Esophageal stenosis	1 (3)
Paralysis recurrent laryngeal nerve	1 (3)
Pelvic infection	1 (3)
Pneumonia aspiration	1 (3)
Pneumonia necrotizing	1 (3)
Pulmonary hematoma	1 (3)
Rhabdomyolysis	1 (3)
Rib fracture	1 (3)
Staphylococcal infection	1 (3)
Stress cardiomyopathy	1 (3)
Syncope	1 (3)

Source: Supplementary Table S1 of 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-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0): https://creativecommons.org/licenses/by-nc-nd/4.0/ [3]

Table 8: Suspected Treatment-Related Serious AEs in the ROAR Trial

Preferred term	(N = 36) n (%)
Any event	7 (19)
Pyrexia	1 (3)
Neutrophil count decreased	2 (6)
Leukopenia	2 (6)

Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Table 9: Summary of Deaths in the ROAR Trial

Cause	(N = 36) n (%)
Died	24 (67)
Alive at last contact, follow-up ended	12 (33)
Time to death from last dose	
≤ 30 days	6 (17)
> 30 days	18 (50)
Primary cause of death	
Non-cardiovascular cause	21 (58)
Disease progression	20 (56)
Pneumonia and pleural effusion, sepsis	1 (3)
Cardiovascular	3 (8)
Pulmonary embolism	1 (3)
Digestive, hemorrhage	1 (3)
Acute respiratory failure	1 (3)

Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Table 10: Study Treatment Discontinuation in the ROAR Trial

Reason for dabrafenib and trametinib discontinuation	(N = 36) n (%)
AE	6 (17%)
Progressive disease	22 (61%)
Study terminated by sponsor	2 (6%)
Withdrawal by patient	6 (17%)

AE = adverse event.

Source: Subbiah et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med.* 2023;29(5):1103-1112. Copyright 2023 by the authors. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10202803/. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en [6]

Table 11: AEs Leading to Treatment Discontinuation, Dose interruption, or Dose Reduction in More than One Patient in the ROAR Trial

Preferred term	(N = 36) n (%)
Leading to discontinuation	6 (17)
Dyspnea	2 (6)
Pleural effusion	2 (6)
Nausea	1 (3)
Ejection fraction decreased	1 (3)
Pneumonia	1 (3)
Acute kidney injury	1 (3)
Aspiration	1 (3)
Conjunctivitis	1 (3)
Diverticulitis	1 (3)
Peripheral edema	1 (3)
Esophageal stenosis	1 (3)
Paralysis recurrent laryngeal nerve	1 (3)
Pericardial effusion	1 (3)
Pneumonia necrotizing	1 (3)
Rhabdomyolysis	1 (3)
Leading to dose interruption	18 (50)
Pyrexia	5 (14)
Pneumonia	3 (8)
Chills	2 (6)
AST increased	2 (6)
Ejection fraction decreased	2 (6)
Neutrophil count decreased	2 (6)
Leukopenia	2 (6)
Nausea	1 (3)
Fatigue	1 (3)
Neutropenia	1 (3)
ALT increased	1 (3)
Rash maculopapular	1 (3)
Vision blurred	1 (3)
Anemia	1 (3)
Urinary tract infection	1 (3)
Asthenia	1 (3)
Atrial fibrillation	1 (3)
Blood AP increased	1 (3)
Pulmonary embolism	1 (3)
Wound infection	1 (3)
Back pain	1 (3)
Clavicle fracture	1 (3)
Dizziness	1 (3)
Facial nerve disorder	1 (3)
Femoral neck fracture	1 (3)
Hallucination	1 (3)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (3)
Hypotension	1 (3)
Oral candidiasis	1 (3)
Pelvic infection	1 (3)
Pleural effusion	1 (3)
Pneumonia aspiration	1 (3)
Pulmonary hematoma	1 (3)
Rib fracture	1 (3)
Skin lesion	1 (3)
Syncope	1 (3)

Weight decreased	1 (3)
Leading to dose reduction	17 (47)
Pyrexia	6 (17)
Fatigue	2 (6)
Neutrophil count decreased	2 (6)
Ejection fraction decreased	2 (6)
Pneumonia	2 (6)
Pneumonitis	2 (6)
WBC count decreased	2 (6)
Chills	1 (3)
Headache	1 (3)
Peripheral edema	1 (3)
ALT increased	1 (3)
Neutropenia	1 (3)
Pruritus	1 (3)
Blood creatinine increased	1 (3)
Dermatitis acneiform	1 (3)
Fungal infection	1 (3)
Cystitis	1 (3)
Dyspepsia	1 (3)
Erythema	1 (3)
Hyponatremia	1 (3)
Pleural effusion	1 (3)
Proteinuria	1 (3)

AE = adverse event; AST = aspartate aminotransferase; WBC = white blood cell.

Source: Supplementary Table S1 of 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-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0): https://creativecommons.org/licenses/by-nc-nd/4.0/ [3]

Table 12: Summary of AEs in the Study by Lorimer et al.

Preferred term	Grade 1 (N = 17) n (%)	Grade 2 (N= 17) n (%)
Breathlessness	5 (30)	2 (12)
Decreased appetite	4 (24)	1 (6)
Fatigue	4 (24)	2 (12)
Oral mucositis	4 (24)	0
Nausea	2 (12)	2 (12)
Skin dryness/itch	2 (12)	2 (12)
Fever	0	4 (24)
Low mood	3 (18)	0
Diarrhea	2 (12)	1 (6)
Eye symptoms	1 (6)	2 (12)
Musculoskeletal pain	2 (12)	0
Constipation	2 (12)	0
Hypertension	1 (6)	0

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.[4]

Table 13: AEs Leading to Dose Interruption in the Study by Lorimer et al.

Cause	(N = 17) n (%)
Pause from treatment	11 (65)
Reason	
A break for surgery	3 (18)
Site infection	1 (6)
Fever	3 (18)
Fatigue and pneumonitis	1 (6)
Muscle cramp	1 (6)
Anemia	1 (6)
Hypocalcaemia	1 (6)
Uveitis	1 (6)

Source: Lorimer et al. (2023)[4]

Table 14: AEs Leading to Dose Reductions in the Study by Lorimer et al.

Cause	(N = 17) n (%)
Dose reduction of 1 or both drugs	9 (53)
Both dabrafenib and trametinib	6 (35)
Only dabrafenib	2 (12)
Only trametinib	1 (6)
Reasons for dose reduction of dabrafenib	
Nausea and uveitis	1 (6)
Pneumonitis and fatigue	1 (6)
Fever	2 (12)
Anemia	1 (6)
Fever and nausea	1 (6)
Reasons for dose reduction of trametinib	
Cramps	1 (6)
Anemia	1 (6)
Poor appetite	1 (6)

Source: Lorimer et al. (2023)[4]

Appendix 7: Cost Comparison Table

The comparators presented in Table 15 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the clinical trial[2,3,6] and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. No comparators to dabrafenib plus trametinib were identified for the treatment of adult patients with BRAF V600E ATC.

The recommended dose of dabrafenib is 150 mg twice daily, while that of trametinib is 2 mg once daily until disease progression or unacceptable toxicity (Table 15). At $75.35 per 75 mg dabrafenib capsule and $342.13 per 2 mg trametinib tablet, the treatment acquisition cost of the dabrafenib plus trametinib regimen is $643.52 daily, or $18,018 per patient per 28 days. Results may differ by jurisdiction depending on individual list prices for the drugs under review in Table 15.

Table 15: CDA-AMC Cost Comparison Table for adults with BRAF V600E mutation anaplastic thyroid cancer

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Cost per 28 days[a]
Dabrafenib (Tafinlar)	50 mg 75 mg	Capsule	50.3255 75.3473	150 mg twice daily until disease progression or intolerable toxicity.	301.39	8,439
Trametinib (Mekinist)	0.5 mg 2 mg	Tablet	86.4933 342.1279	2 mg once daily until disease progression or intolerable toxicity.	342.13	9,580
Dabrafenib + trametinib					643.52	18,018

Note: All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (accessed Jan 2025),[7] and do not include dispensing fees.

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